Document Title

Summary of the toxicological studies for Bixafen + Fluopyram + Prothioconazole EC 260 (65+65+130 g/L)

Data Requirement(s)

Regulation (EC) No 1107/2009 & Regulation (EU) No 284/2013

Document MCP

Section 7: Toxicological studies

According to the Guidance Document SANCO/10181/2013 for applicants on preparing dossiers for the approval of a chemical active substance

Date

2021-03-22

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Bayer AG

Crop Science Division

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Version history

Date [yyyy-mm-dd]	Data points containing amendments or additions[1] and brief description	Document identifier and version number

[1] It is suggested that applicants adopt a similar approach to showing revisions and version history as outlined in SANCO/10180/2013 Chapter 4, 'How to revise an Assessment Report'.

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CP 7 TOXICOLOGICAL STUDIES ON THE PLANT PROTECTION PRODUCT

Fluopyram was included in Annex I to Council Directive 91/414/EEC in 2013 (Regulation (EU) 802/2013 into Force on August 22nd, 2013). This Supplementary Dossier contains only data which were not submitted at the time of the Annex I inclusion of Fluopyram under Council Directive 91/414/EEC and which were therefore not evaluated during the first EU review. All data which were already submitted by Bayer AG (former Bayer CropScience) for the Annex I inclusion under Council Directive 91/414/EEC are contained in the Draft Assessment Report (DAR) and its Addenda and are included in the Baseline Dossier provided by Bayer.

The formulation bixafen + fluopyram + prothioconazole EC 260 (65+65+130 g/L), abbreviation BIX+FLU+PTZ EC 260 (65+65+130), is an Emulsion Concentrate (EC) formulation containing 65 g/L of bixafen, 65 g/L fluopyram and 130 g/L prothioconazole. This formulation is registered throughout Europe under trade names such as ASCRA XPRO, Macfare Xpro and Veldig XPRO. BIX+FLU+PTZ EC 260 (65+65+130) was not already a representative formulation of Bayer AG for the Annex I inclusion of Fluopyram under Council Directive 91/414/EEC.

CP 7.1 Acute toxicity

The acute toxicity studies have been conducted with formulation Bixafen+fluopyram+prothioconazole EC 65+65+130 g/L (abbreviation: BIX+FLU+PTZ EC 260) (specification 102000027828, batch 2013-002135), the in vivo studies were also required for registration in regions outside of the EU.

BIX+FLU+PTZ EC 260 is of low toxicity by the oral route of exposure in the Wistar rat and non-toxic by the dermal route of exposure in the Wistar rat. The formulation is not irritating when applied to the skin of NZW rabbits. BIX+FLU+PTZ EC 260 applied to the rabbits' eye mucosa, caused significant conjunctival and corneal irritant effects at 1 hour after application. The conjunctival and corneal effects were not reversible at the end of the observation period. BIX+FLU+PTZ EC 260 was shown to have sensitization potential (sensitizer) in the Local Lymph Node Assay. A rationale is presented under CP 7.1.3 as to why acute testing via the inhalation route is not required.

The active substances bixafen, fluopyram and prothioconazole do not require classification for health affects according to Regulation (EC) No 1272/2008.

Classification/labelling based on the toxicological studies and all submitted data:

- Regulation (EC) No 1272/2008 (CLP):
  - Acute Tox. 4 / H302: Harmful if swallowed
  - Eye Dam. 1 / H318: Causes serious eye damage
  - Skin Sens. 1B / H317: May cause an allergic skin reaction

Table 7.1- 1: Acute toxicity studies with BIX+FLU+PTZ EC 260

Study Type	Species	Results	Reference
Acute oral toxicity	Rat	LD_{50} > 300 < 2000 mg/kg bw	M-463048-01-1
Acute dermal toxicity	Rat	LD_{50} > 2000 mg/kg bw	M-461508-01-1
Skin irritation	Rabbit	Not irritating	M-461510-01-1
Eye irritation	Rabbit	Significant eye irritation	M-463964-01-1
Skin sensitisation LLNA	Mouse	Sensitizing	M-467203-01-1

CP 7.1.1 Oral toxicity

Data Point:	KCP 7.1.1/01
Report Author:	[redacted]
Report Year:	2013
Report Title:	Bixafen+fluopyram+prothioconazole EC 65+65+130 g/L - Acute oral toxicity study in rats
Report No:	13/137-001P
Document No:	M-463048-01-1
Guideline(s) followed in study:	OECD 423; EEC Directive 440/2008, B.1.tris; US-EPA 712-C-98-190, OPPTS 870.1100
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: Bixafen+fluopyram+prothioconazole EC 65+65+130 g/L
Abbreviation: BIX+FLU+PTZ EC 260

Specification no.:	102000027828-01
Description:	Clear brown, liquid
Lot/Batch no.:	2013-002135
Content:	Bixafen (BYF 00587): 6.49% w/w, 65.61 g/L Fluopyram (AE C656948): 6.35% w/w, 64.21 g/L Prothioconazole (JAU 6476):12.7% w/w, 128.5 g/L
Stability of test compound:	Guaranteed for study duration; expiry date: 02 May 2015

2. Vehicle: Distilled water

3. Test animals

Species:	Wistar rat SPF
Strain:	RccHan
Age:	10 weeks
Weight at dosing:	176 - 196 g
Source:	[redacted]
Acclimatisation period:	At least 20 days
Diet:	Ssniff® SM R/M produced by ssniff Spezialdiäten GmbH, D-59494 Soest, Germany, *ad libitum*
Water:	Tap water

Housing: 3 animals/cage
Type II polypropylene/polycarbonate
Lignocel Bedding for Laboratory Animals was available to animals during the study

B. Study design and methods

1. Animal assignment and treatment

Dose: Initially, three females (assigned to Group 1) were treated at a dose level of 2000 mg/kg bw. The test item caused mortality in this group (2/3). Therefore a second group (Group 2) was treated at a dose level of 300 mg/kg bw. As no mortality was observed, a confirmatory group (Group 3) was treated at the same dose level.

Application route/exposure: Single oral gavage dose

Application volume: 10 mL/kg bw

Fasting time: Food, but not water, was withheld during an overnight period. Food was made available again 3 hours after the treatment.

Group size: 3 females

Post-treatment observation period: 14 days

Observations: Mortality, clinical signs, body weight, gross necropsy

II. Results and discussion

A. Mortality

Table 7.1.1-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological result*	Occurrence of signs	Time of death	Mortality (%)
Female rats				
Group 1: 2000	2 / 3 / 3	First onset of signs 30 mins after dosing	One animal died on day 1 and one animal on day 2	66.7%
Group 2: 300	0 / 0 / 3	No signs	No deaths	0
Group 3: 300	0 / 0 / 3	No signs	No deaths	0
* number of animals which died spontaneously and/or were sacrificed in moribund state / number of animals with signs of toxicity / total number of animals used per group				
LD_{50} > 2000 mg/kg bw				

B. Clinical observations

Clinical signs were observed in animals treated at 2000 mg/kg bw with BIX+FLU+PTZ EC 260. These included decreased activity (3/3), hunched back (3/3), prone position (3/3), piloerection (2/3), cold to touch (1/3), respiratory rate decreased (2/3) and death (2/3).

No clinical signs were observed in all animals at 300 mg/kg bw.

C. Body weight

Body weight and body weight gain of BIX+FLU+PTZ EC 260 treated animals showed no indication of a treatment-related effect.

D. Necropsy

In female 1509 (2000 mg/kg bw) dark red foci on the glandular mucosa of the stomach, in female 1510 (2000 mg/kg bw), yellow, liquid material in the stomach, duodenum and jejunum, brown, liquid content in the urinary bladder were noted at necropsy and was regarded as potentially related to the administration of the test item. Red discolorations of the non-collapsed lungs were also noted in these animals at necropsy.

In the animals, dosed at 300 mg/kg bw no test-item related macroscopic changes could be noted.

III. Conclusion

Under the conditions of this study, the acute oral LD_{50} value of the test item BIX+FLU+PTZ EC 260 was found to be between 300 and 2000 mg/kg bw in female RccMan:WIST rats.

The study result triggers the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP): Acute Tox. 4 / H302: Harmful if swallowed

Assessment and conclusion by applicant:

Study meets the current guidance and the requirements in 283/2013. The acute oral LD_{50} value was found to be between 300 and 2000 mg/kg bw triggering classification as Harmful under Regulation (EC) No 1272/2008 (CLP).

CP 7.1.2 Dermal toxicity

Data Point:	KCP 7.1.2.01
Report Author:	[redacted]
Report Year:	2013
Report Title:	Bixafen+fluopyram+prothioconazole EC 65+65+130 g/L - Acute dermal toxicity study in rats
Report No:	13137-602P
Document No:	M-461508-01-1
Guideline(s) followed in study:	OECD 402; US-EPA 712-C-98-192, OPPTS 870.1200; EC 440/2008, B.3
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: Bixafen+fluopyram+prothioconazole EC 65+65+130 g/L

Abbreviation: BIX+FLU+PTZ EC 260

Specification no.: 000027828-01

Description:	Clear brown, liquid
Lot/Batch no.:	2013-002135
Content:	Bixafen (BYF 00587): 6.49% w/w, 65.61 g/L Fluopyram (AE C656948): 6.35% w/w, 64.21 g/L Prothioconazole (JAU 6476): 12.7% w/w, 128.5 g/L
Stability of test compound:	Guaranteed for study duration; expiry date: 2 May 2015

2. Vehicle: None

3. Test animals

Species:	Wistar rat; SPF
Strain:	RccHan
Age:	Young adult rats
Weight at dosing:	208 - 236 g
Source:	[redacted]
Acclimatisation period:	7 days
Diet:	Ssniff® SM R/M produced by ssniff Spezialdiäten GmbH, D-59494 Soest, Germany, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Individual caging Type II. polypropylene/polycarbonate Lignocel Bedding for Laboratory Animals was available to animals during the study, *ad libitum*

B. Study design and methods

1. Animal assignment and treatment

Dose:	Dose (mg/kg bw)		Surface area
	males	2000	5 x 5 cm
	females	2000	5 x 5 cm
Application route:	Dermal, semi-occlusive dressing		
Exposure:	24 hours		
Group size:	5 rats/sex/group		
Post-treatment observation period:	14 days		
Observations:	Mortality, clinical signs, body weight, gross necropsy		

II. Results and discussion

A. Mortality

Table 7.1.2-1 Doses, mortality / animals treated

Dose (mg/kg bw)	Toxicological results*	Occurrence of signs	Time of death	Mortality (%)
Male rats				
2000	0 / 0 / 5	No signs	No deaths	0
Female rats				
2000	0 / 0 / 5	No signs	No deaths	0
* number of animals which died spontaneously and/or were sacrificed in moribund state / number of animals with signs of toxicity / total number of animals used per group				
LD_{50} > 2000 mg/kg bw				

B. Clinical observations

No clinical signs were observed after treatment with the test item during the 14 day observation period. No local dermal signs were observed after treatment with the test item during the 14 day observation period.

C. Body weight

There were no treatment related effects on body weight or body weight gain during the observation period.

D. Necropsy

There was no evidence of any observations at a dose level of 2000 mg/kg bw at necropsy.

III. Conclusion

The median lethal dose of BIX+FLU+PTZ EC 260 after a single dermal administration was found to be greater than 2000 mg/kg bw in male and female RccHan:WIST rats.

The study result triggers the following classification/labelling:

Regulation (EC) No 1272/2008 (CLP): none

Assessment and conclusion by applicant:

Study meets the current guidance and the requirements in 283/2013. Acute toxicity via the dermal route is low in the rat. The LD_{50} value was > 2000 mg/kg bw and does not trigger classification

CP 7.1.3 Inhalation toxicity

Since BIX+FLU+PTZ EC 260 is commercialized in the form of an emulsifiable concentrate formulation, which is a liquid; no acute inhalation study is required. The neat formulation will not be used in a manner that is expected to pose any acute inhalation hazard. The vapor pressure at 25°C is 3.9×10^{-7} Pa for bixafen, 3.1×10^{-6} Pa for fluopyram and $<<4 \times 10^{-7}$ for prothioconazole.

With respect to Regulation (EC) No 1107/2009, as well as Commission Regulation (EU) No 284/2013, testing for the acute inhalation toxicity of BIX+FLU+PTZ EC 260 is not triggered because it:

- is not a gas or liquefied gas,
- is not a smoke generating formulation or fumigant,
- is not to be used with fogging equipment,
- is not a vapour releasing preparation,
- is not an aerosol,
- is not a powder, is dust-free, and hence does not contain a significant proportion of particles of diameter < 50 µm (> 1 % on a weight basis),
- is not to be applied from aircraft and
- does not contain active substances with a vapour pressure > 1 x 10-2 Pa and
- is not to be used in a manner which generates a significant proportion of particles or droplets of diameter < 50 µm (>1% on a weight basis).

In the absence of the need to perform an acute inhalation toxicity study the BIX+FLU+PTZ EC 260 formulation needs not be classified.

BIX+FLU+PTZ EC 260 triggers the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP): none

Assessment and conclusion by applicant:

Due to the physical chemical properties of the product and the use pattern a study to investigate acute inhalation toxicity was not triggered. The formulation need not be classified for of acute inhalation.

CP 7.1.4 Skin irritation

Data Point:	KCP 7.1.4/01
Report Author:	[redacted]
Report Year:	2013
Report Title:	Bixafen+fluopyram+prothioconazole EC 65+65+130 g/L - Acute skin irritation study in rabbits
Report No:	13/137-006N
Document No:	M-461510-01-1
Guideline(s) followed in study:	OECD 404; US-EPA 712-C-98-196, OPPTS 870.2500; Commission Regulation (EC) No 440/2008, B.4
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: Bixafen+fluopyram+prothioconazole EC 65+65+130 g/L
Abbreviation: BIX+FLU+PTZ EC 260

Specification no.:	102000027878-01
Description:	Clear brown, liquid
Lot/Batch no.:	2013002135
Content:	Bixafen (BYF 00387): 6.49% w/w, 65.61 g/L Fluopyram (AE C656948): 6.35% w/w, 64.21 g/L Prothioconazole (JAU 6476): 12.7% w/w, 128.5 g/L
Stability of test compound:	Guaranteed for study duration; expiry date: 2 May 2015

2. Vehicle: None

3. Test animals

Species:	Rabbit
Strain:	New Zealand White
Age:	Approx. 12 weeks
Weight at dosing:	3.0 - 3.1 kg
Source:	[redacted]
Acclimatisation period:	13 days
Diet:	Uni diet for rabbits produced by Agribrands Europe Hungary PLC, H-5300 Karcag, Madarasi út, Hungary, *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Individually housed in AAALAC approved metal wire rabbit cages

B. Study design and methods

1. Animal assignment and treatment

Dose:	0.5 mL/patch
Application route:	Dermal
Exposure:	4 hours
Group size:	3 females
Observations:	Skin effects, clinical signs, body weight

II. Results and discussion

A. Findings

No clinical signs of systemic toxicity were observed in the animals during the study and no mortality occurred. The body weights of all rabbits were considered to be within the normal range of variability.

As no clinical signs and no skin irritation effects were observed at 72 hours after patch removal, the study was terminated after the 72 hours observation.

Table 7.1.4-1 Summary of irritant effects (Scores)

Animal	Observation (after patch removal)	24h	48h	72h	Mean scores	Response	Reversible (days)
00385	Erythema (redness) and eschar formation	0	0	0	0.0	--	na
	Oedema formation	0	0	0	0.0	--	na
01294	Erythema (redness) and eschar formation	0	0	0	0.0	--	na
	Oedema formation	0	0	0	0.0	--	na
01255	Erythema (redness) and eschar formation	0	0	0	0.0	--	na
	Oedema formation	0	0	0	0.0	--	na

na = not applicable

Response:			
--	= negative for mean scores	<1.5	(GHS)
		<2.3	(Regulation (EC) No 1272/2008)
(+)	= mild irritant for mean scores	≥1.5 - <2.3	(GHS category 3)
+	= irritant for mean scores	≥2.3	(Regulation (EC) No 1272/2008 and GHS category 2)

III. Conclusion

BIX+FLU+PTZ EC 260 is not irritating to the skin according to the Draize classification system.

The study result triggers the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP): none

Assessment and conclusion by applicant:

Study meets the current guidance and the requirements in 283/2013. The product does not provoke skin irritation and the results do not trigger classification.

CP 7.1.5 Eye irritation

Data Point:	KCP 7.1.5/01
Report Author:	[redacted]
Report Year:	2013
Report Title:	Bixafen+fluopyram+prothioconazole EC 65+65+130 g/L - Acute eye irritation study in rabbits
Report No:	13/137-005N
Document No:	M-463964-01-1
Guideline(s) followed in study:	OECD 405; US-EPA 712-C-98-195, OPPTS 870.2400; Commission Regulation (EC) No 440/2008, B.5
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: Bixafen+fluopyram+prothioconazole EC 65+65+130 g/L

Abbreviation: BIX+FLU+PTZ EC 260

Specification no.: 102000027828-01

Description: Clear brown, liquid

Lot/Batch no.: 2013-002135

Content: Bixafen (BYF 00587): 6.49% w/w, 65.61 g/L
Fluopyram (AE C656948): 6.35% w/w, 64.21 g/L
Prothioconazole (JAU 6476): 12.7% w/w, 128.5 g/L

Stability of test compound: Guaranteed for study duration; expiry date: 2 May 2015

2. Vehicle: None

3. Test animals

Species: Rabbit

Strain: New Zealand white

Age: 11-12 weeks old

Weight at dosing: 2.9 - 3.0 kg

Source: [redacted]

Acclimatisation period: At least 6 days

Diet: UNI diet for rabbits produced by AGRIBRANDS Europe Hungary PLC, H-5300 Karcag, Madarasi út, Hungary, *ad libitum*

Water: Tap water, *ad libitum*

Housing: Individually housed in AAALAC approved metal wire rabbit cages

B. Study design and methods

1. Animal assignment and treatment

Dose:	0.1 mL in one eye/animal
Application route:	Instillation into the conjunctival sac
Rinsing:	The first observation (one hour)
Group size:	3 males
Observations:	Eye effects, clinical signs, body weight

II. Results and discussion

A. Findings

There was no mortality observed during the study. The body weight and body weight changes were considered to be normal with no indication of any treatment related effect.

The general state and behaviour of animals were normal throughout the study period.

Table 7.1.5-1 Summary of Irritant Effects (Scores)

Animal	Effects	24 h	48 h	72 h	Mean scores	Response	Reversible (days)
00344	Corneal opacity	1	1	1	1.00	++	not reversible
	Iritis	0	0	0	0.00	--	na
	Redness conjunctivae	2	2	2	2.00	++	not reversible
	Chemosis conjunctivae	1	1	1	1.00	+	21
	Discharge	2	2	2	2.00	na	21
00333	Corneal opacity	1	1	1	1.00	++	not reversible
	Iritis	0	0	0	0.00	--	na
	Redness conjunctivae	2	2	2	2.00	++	not reversible
	Chemosis conjunctivae	2	2	2	2.00	+	21
	Discharge	3	2	2	2.33	na	14
01752	Corneal opacity	1	1	1	1.00	+	14
	Iritis	0	0	0	0.00	--	na
	Redness conjunctivae	3	3	2	2.00	++	na
	Chemosis conjunctivae	3	3	2	2.67	++	not reversible
	Discharge	3	3	3	3.00	na	not reversible

Na: not applicable

Response for mean scores:		Corneal opacity	Iritis	Conjunctival redness	Conjunctival oedema	
--	= negative	<1	<1	<2	<2	Regulation (EC) No. 1272/2008 and GHS
(+)	= mild irritant	≥1 - <3	≥1 - <2	≥2	≥2	GHS category 2B (effects reversible within 7 days)
+	= irritant	≥1 - <3	≥1 - <2	≥2	≥2	Regulation (EC) No. 1272/2008 (GHS) category 2
++	= irreversible effects/ serious damage	≥3	≥1.5			Regulation (EC) No. 1272/2008 and GHS category 1

III. Conclusion

BIX+FLU+PTZ EC 260 applied to the rabbits' eye mucosa, caused significant conjunctival and corneal irritant effects at 1 hour after application. The conjunctival and corneal effects were not

reversible at the end of the observation period.

The study result triggers the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP) : Eye Dam. 1 / H318: Causes serious eye damage

Assessment and conclusion by applicant:

Study meets the current guidance and the requirements in 283/2013. The product caused significant eye irritation. Results trigger classification under Regulation (EC) No 1272/2008 (CLP) as Eye Dam. 1 / H318.

CP 7.1.6 Skin sensitization

Data Point:	KCP 7.1.6/01
Report Author:	[redacted]
Report Year:	2013
Report Title:	Bixafen + fluopyram + prothioconazole EC 65+65+130 g/L - Local lymph node assay in the mouse
Report No:	13/137-037E
Document No:	M-487203-01-1
Guideline(s) followed in study:	OECD Guideline for Testing of Chemicals No. 429, Skin Sensitisation: Local Lymph Node Assay" Adopted: 22 July 2010 Commission Regulation (EC) No 440/2008 of 30 May 2008, B.42., Skin Sensitisation: Local Lymph Node Assay (Official Journal L142, 31/05/2008)
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I. Materials and methods

A. Materials

1. Test material: Bixafen+fluopyram+prothioconazole EC 65+65+130 g/L

Abbreviation: BIX+FLU+PTZ EC 260

Specification no.: 1020000027828 - 01

Description: Clear brown liquid

Lot/Batch no: 2013-002135

Content: Bixafen (BYF 00587): 6.49% w/w, 65.61 g/L

Fluopyram (AE C656948): 6.35% w/w, 64.21 g/L

Prothioconazole (JAU 6476): 12.7% w/w, 128.5 g/L

Stability of test compound: Guaranteed for study duration; expiry date: 2 May 2015

2. Vehicle: 1% aqueous Pluronic® PE9200

3. Test animals

Species: Mouse

Strain:	CBA/ J Rj
Age:	9 weeks
Weight at dosing:	21 - 23 g
Source:	[redacted]
Acclimatisation period:	13 days
Diet:	Ssniff® SM Rat/Mouse produced by ssniff Spezialdiäten GmbH (Ferdinand-Gabriel-Weg 16, D-59494 Soest, Germany), *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Group caging, type II, polypropylene/ polycarbonate; mice were provided with glass tunnel-tubes, bedding (certified wood chips) was available during the study.

B. Study design and methods

1. Animal assignment and treatment

Dose:	Preliminary study: 50% - 100% Main study: 0% - 25% - 50% - 100%
Application route:	Topically applied onto the dorsal surface of both ears
Application volume:	25 µL/ear
Exposure:	Three consecutive days (day 1, day 2, day 3)
Group size:	Preliminary study: 2 females/dose Main study: 4 females/group
Observations:	Preliminary irritation/toxicity test: daily clinical observation (local irritation and systemic toxicity); initial and terminal body weight; ear thickness (day 1, 3 and 6) and ear punch (biopsy) weight (day 6). Main study: Clinical observation (local irritation and systemic toxicity) initial and terminal body weight. On Day 6, the cell proliferation in the local lymph nodes was measured by incorporation of tritiated methyl thymidine (3HTdR) and the values obtained were used to calculate stimulation indices (SI).

II. Results and discussion

A. Findings

The preliminary irritation/toxicity test showed that the applicability and biocompatibility of the test item on the ears of animals at the maximum concentration of test item was acceptable.

No mortality or systemic toxicity was observed during the study.

There were no indications of any irritancy at the site of application.

No treatment related effects were observed on animal body weights in any test item treated groups. Marked body weight loss was observed in the negative control group for one animal (-5.3 %).

Appearance of the lymph nodes was normal in the negative control group. Larger than normal lymph nodes were observed in the positive control group and in all treated groups (subjective judgement by analogy with observations of former experiments).

The stimulation index values were 16.0, 8.2 and 2.7 at concentrations of 100 % (undiluted), 50 % and 25 % (w/v), respectively (Refer to Figure 7.1.6-1).

Since, there were no confounding effects of irritation or systemic toxicity at the applied concentrations, the proliferation values obtained are considered to reflect the real potential of the test item to cause lymphoproliferation in the Local Lymph Node Assay.

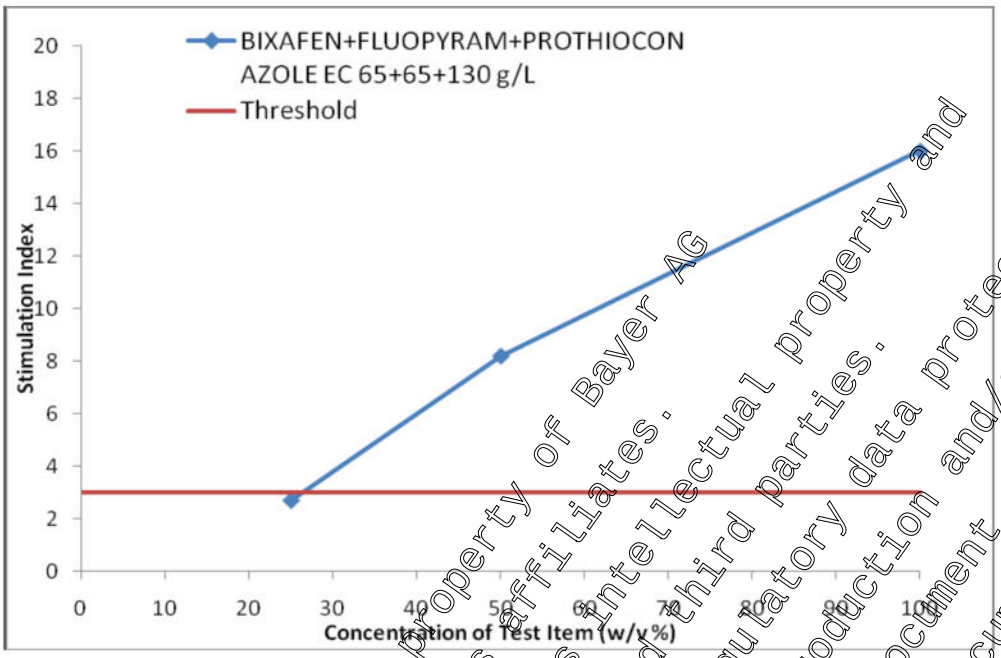
Based on these data, the calculated EC3 value for this test item is 26.4% (Refer to Figure 7.1.6-1).

α-Hexylcinnamaldehyde (25% (w/v) dissolved in 1% Pluronic) was used as a positive control to demonstrate the appropriate performance of the assay. A significant lymphoproliferative response (stimulation index value of 14.8) was noted for the positive control chemical and this result confirmed the validity of the assay.

Table 7.1.6-1 DPM, DPN and Stimulation Index Values for all Groups

Test Group Name	Measured DPM / group	DPM	Number of lymph nodes	DPN	Stimulation Index
Background (5% (w/v) Trichloroacetic acid (TCA))	31.5	-	-	-	-
Negative control (1% Pluronic)	1210	1178.5	8	147.3	1.0
BIX+FLU+PTZ EC 260 100% (undiluted)	18846	18814.5	8	2351.8	16.0
BIX+FLU+PTZ EC 260 50% (w/v) in 1% Pluronic	9742	9710.5	8	1213.8	8.2
BIX+FLU+PTZ EC 260 25% (w/v) in 1% Pluronic	3210	3178.5	8	397.3	2.7
Positive control (25% HCA in 1% Pluronic)	17429	17397.5	8	2174.7	14.8

Figure 7.1.6-1 Test Item Stimulation Index Values



III. Conclusion

In conclusion, under the conditions of the present assay BIX+FLU+PTZ EC 260 was shown to have sensitization potential (sensitizer) in the Local Lymph Node Assay. As the calculated EC3 value for this test item of 26.4% is > 2%, classification Category 1, sub-category 1B is required

The study result triggers the following classification/labelling:

- Regulation (EC) No 1272/2008 (CLP): Skin Sens. 1B / H317: May cause allergic skin reaction

Assessment and conclusion by applicant:

Study meets the current guidance and the requirements in 283/2013. The product showed skin sensitization potential. Results trigger classification under Regulation (EC) No 1272/2008 (CLP) as Skin Sens. 1B / H317.

CP 7.1.7 Supplementary studies on the plant protection product

No such studies are necessary since there are no concerns arising, e.g., from potential synergistic or additive effects exerted by the active substance(s) or other components in Bixafen + Fluopyram + Prothioconazole EC 260 (65+65+130 g/L) that would require further investigations.

CP 7.1.8 Supplementary studies for combinations of plant protection products

No such studies are necessary since Bixafen + Fluopyram + Prothioconazole EC 260 (65+65+130 g/L) is not intended for use in combination with other plant protection products.

CP 7.2 Data on exposure

Evaluations of the exposure of operators, bystanders, residents and re-entry workers to Fluopyram when used in the BIX + FLU + PTZ EC 260 formulation are provided in the following sections. It is known that after application of prothioconazole-containing products diluted prothioconazole can degrade to prothioconazole-desthio on surfaces, clothing or skin. Accordingly, although prothioconazole-desthio is not part of the formulation per se, non-dietary risk assessments are always performed for prothioconazole-desthio due to its toxicological properties.

Table 1: Product information and toxicological reference values used for the exposure assessment

Product	BIX+FLU+PTZ EC 260 (65+65+130)
Formulation type	Soluble concentrates, emulsifiable concentrate, etc.

Active substance(s) (incl. content)	**Substance Concentration** [g/L or g/kg]	**AOEL$_{systemic}$ (RVNAS)** [mg/kg bw/d]	**AAOEL (RVAAS)** [mg/kg bw/d]	**Inhalation absorption [%]**	**Oral absorption [%]**	**Dermal absorption***	
						Concentrate **[%]**	Dilution **[%]**
Fluopyram (FLU)	65	0.05	-	100	100	25	70
Prothioconazole (PTZ)	130	0.2	-	100	100	25	70
Bixafen (BIX)	65	0.13	-	100	100	25	70
Prothioconazole-deathio (PTZ-desthio) **	117.9	0.01	-	100	100	-	44

For more information please refer to chapter CP 7.3

** *Concentrate: not applicable (prothioconazole-desthio is not present in the product, it can be formed during and after the application of dilutions during the drying process)*

Selection of representative use and justification

The critical GAP(s) used for the exposure assessment of the plant protection product is/are shown in A list of all intended uses within the zone/ EU is given in Part B, Section 0.

Table 2: Critical uses and overall conclusion of exposure assessment

1	2	3	4	5	6	7	8	9	10			
Use-No.*	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I ****	**Application**		**Application rate**		**PHI (d)**	**Remarks: (e.g. safener/synergist (L/ha)) critical gap for operator, worker, bystander or resident exposure based on [Exposure model]**	**Acceptability of exposure assessment**			
			Method / Kind (incl. application technique ***)	**Max. number (min. interval between applications) a) per use b) per crop/ season**	**Max. application rate kg as/ha a) a.s. 1 b) a.s. 2 c) a.s. 3**	**Water L/ha min / max**			**Operator**	**Worker**	**Bystander**	**Residents**
4	Barley (HORVX) (BBCH 30-61)	F	spraying (broadcast, overall) LCTM	a) 1 (-) b) 1 (-)	a) FLU 78 b) BIX 78 c) PTZ 156	200 – 400	As per growth stage	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874				

* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1
** F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application
*** e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held

Justification

The chosen Gap covers the representative use in the scope of operator, resident/bystander and worker exposure.

CP 7.2.1 Operator exposure

CP 7.2.1.1 Estimation of operator exposure

A summary of the exposure models used for the estimation of operator exposure to the active substance(s) during application of BIX+FLU+PTZ EC 260 according to the critical use(s) is presented in the following tables.

Since the conversion rate of Prothioconazole to prothioconazole-desthio is not known, a conservative approach was applied and the following assumptions were used in the exposure calculations for the exposure risk of operators to prothioconazole-desthio:

- For the exposure assessment to prothioconazole-desthio a 100% conversion of Prothioconazole to prothioconazole-desthio is assumed. When calculating the amount of prothioconazole-desthio a conversion factor of 0.907 is applied (based on a molecular weight of 344.254 g/mol for Prothioconazole and 312.194 g/mol for prothioconazole-desthio). Formation of prothioconazole-desthio is not expected in the concentrate, thus during the M/L task dermal absorption of prothioconazole-desthio was not considered and a dermal absorption value of 0% for the concentrate was applied to remove this from calculation. Although either not expected inhalation exposure is still considered for the M/L task since the EFSA calculator does not allow the elimination without deeper manipulation of the calculator.
- No conversion of Prothioconazole to prothioconazole-desthio was considered for the exposure assessment to Prothioconazole.

As mentioned so far, no model is available to estimate the conversion of prothioconazole to prothioconazole-desthio in a realistic manner. Accordingly, the risk assessments should always consider measured data whenever such data are available. Therefore, three operator exposure studies were conducted to determine the exposure Prothioconazole as well as to prothioconazole-desthio under real use conditions and thus to get a better basis for a realistic risk assessment.

Table 3: Exposure models for intended uses

Critical use(s)	1.2 L / kg product/ha for Cereals
Model(s)	*Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal 2014;12(10):3874*

The outcome of the estimation is presented in the following table(s).

Table 4: Estimated operator exposure, Fluopyram, Cereals

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Outdoor, Downward spraying, Vehicle-mounted Application rate: 0.078 kg a.s./ha			
EFSA Operator Model (75th quantile regression)	no PPE[2]	0.066	132
	with PPE[3]	0.00297	5.93

[1] AOEL (RVNAS) of FLU: 0.05 mg/kg bw/day
[2] no PPE: Work wear - arms, body and legs covered
[3] with PPE: Work wear - arms, body and legs covered. In addition, gloves during mixing and loading and when handling contaminated surfaces during application.

Table 5: Estimated operator exposure, Bixafen, Cereals

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Outdoor, Downward spraying, Vehicle-mounted Application rate: 0.078 kg a.s./ha			
EFSA Operator Model (75th quantile regression)	no PPE[2]	0.066	50.8
	with PPE[3]	0.00297	2.28

[1] AOEL (RVNAS) of BIX: 0.13 mg/kg bw/day
[2] no PPE: Work wear - arms, body and legs covered
[3] with PPE: Work wear - arms, body and legs covered. In addition gloves during mixing and loading and when handling contaminated surfaces during application.

Table 6: Estimated operator exposure, Prothioconazole, Cereals

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Outdoor, Downward spraying, Vehicle-mounted Application rate: 0.156 kg a.s./ha			
EFSA Operator Model (75th quantile regression)	no PPE[2]	0.115	57.5
	with PPE[3]	0.00508	2.54

[1] AOEL (RVNAS) of PTZ: 0.2 mg/kg bw/day
[2] no PPE: Work wear - arms, body and legs covered
[3] with PPE: Work wear - arms, body and legs covered. In addition gloves during mixing and loading and when handling contaminated surfaces during application.

Table 7: Estimated operator exposure, PTZ-Desthio, Cereals

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Outdoor, Downward spraying, Vehicle-mounted Application rate: 0.141 kg a.s./ha			
EFSA Operator Model (75th quantile regression)	no PPE[2]	0.00817	81.7
	with PPE[3]	0.00138	13.8

[1] AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
[2] no PPE: Work wear - arms, body and legs covered
[3] with PPE: Work wear - arms, body and legs covered. In addition gloves during mixing and loading and when handling contaminated surfaces during application.

Conclusion

The operator exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and considering above mentioned personal protective equipment (PPE).
Based on the presented calculation it is demonstrated that no unacceptable risk is given with the intended use of BIX+FLU+PTZ EC 260.

CP 7.2.1.2 Measurement of operator exposure

As mentioned before it has been found that Prothioconazole in diluted solutions can convert to prothioconazole-desthio (other internal code: SXX 0665) during the drying process on clothing, skin or on certain plant surfaces. The conversion product, prothioconazole-desthio is known to have an embryotoxic potential in experimental animals. Therefore, three operator exposure studies were conducted to determine the exposure to prothioconazole as well as to prothioconazole-desthio under real use conditions and thus to get a better basis for a realistic risk assessment.
The first study was already submitted and evaluated for Annex I inclusion of prothioconazole. Since then BCS has conducted two further exposure studies with twelve farmers under real and representative conditions in cereals and canola.

As being the RMS for prothioconazole at that time all operator exposure studies have been (re-) evaluated by the UK during the AIR process for prothioconazole. For details please refer to the draft renewal assessment report for Prothioconazole, which is publicly available on the EFSA webpage[1]. For the sake of transparency and value traceability the study evaluation procedure described in this chapter follows the approach taken by the UK, even though the applicant disagrees with some evaluation points:

The studies are also part of the new AOEM Model (EFSA Model for operator exposure). However, as the studies were set up as mixer/loader/applicator studies only part of the data are used in the model. In addition, the data in the model are used as prothioconazole-equivalents (sum of exposures to

[1] EFSA: Public consultation on the active substance prothioconazole: https://www.efsa.europa.eu/de/consultations/call/180612

prothioconazole and prothioconazole-desthio) and, hence, do not allow to distinguish between exposure to prothioconazole and prothioconazole-desthio.
Concerning exposure to prothioconazole-desthio the outcome of the estimations is presented in the following table. For details please refer to Details on the studies.

Table 8: Estimated operator exposure, prothioconazole-desthio, Cereals

Model data	Level of PPE	Total absorbed dose (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
Outdoor, Downward spraying, Vehicle-mounted Application rate: 0.141 kg PTZ/ha			
Measurement of exposure, Parametric 75th percentile	with PPE[2]	0.000432	4.32

1 AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day

2 with PPE: Work wear - arms, body and legs covered, In addition gloves during mixing and loading and when handling contaminated surfaces during application.

Operator exposure calculations (KCP 7.2.1.1)

Table 9: Operator exposure, Fluopyram, Cereals, no PPE / with PPE

Substance	Fluopyram	**Formulation** = Soluble concentrates, emulsifiable concentrate, etc.	**Application rate** = 0.078 kg a.s. /ha	**Spray dilution** = 0.39 g a.s./l	**Vapour pressure** = low volatile substances having a vapour pressure of < 1*10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer** = 2-3 m	**Number of applications** = 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral** = 100%	**Inhalation** = 100%	
RVNAS[1] (AOEL)	0.05 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	

Operator Model		Mixing, loading and application AOEM			
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.108		% of RVNAS[1]	216%
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%
Mixing and Loading		**Gloves = Yes**	Clothing = Work wear arms, body and legs covered	PPE = None	Soluble bags = No
Application		**Gloves = Yes**	Clothing = Work wear arms, body and legs covered	PPE = None	Closed cabin = No
Exposure (Workwear)	Longer term systemic exposure mg/kg bw/day	**0.066**		% of RVNAS[1]	**132%**
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%
Exposure (Including PPE options above)	Longer term systemic exposure mg/kg bw/day	**0.00297**		% of RVNAS[1]	**5.93%**
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 10: Operator exposure, Bixafen, Cereals, no PPE / with PPE

Substance	Bixafen	**Formulation** = Soluble concentrates, emulsifiable concentrate, etc.	**Application rate** = 0.078 kg a.s. /ha	**Spray dilution** = 0.39 g a.s./l	**Vapour pressure** = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer** = 2-3 m	**Number of applications** = 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral** = 100%	**Inhalation** = 100%	
RVNAS[1] (AOEL)	0.13 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	

Operator Model	Mixing, loading and application AOEM				
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.208		% of RVNAS[1]	83.1%
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%
Mixing and Loading	**Gloves = Yes**	Clothing = Work wear - arms, body and legs covered		PPE = None	Soluble bags = No
Application	**Gloves = Yes**	Clothing = Work wear - arms, body and legs covered		PPE = None	Closed cabin = No
Exposure (Workwear)	Longer term systemic exposure mg/kg bw/day	**0.066**		% of RVNAS[1]	**50.8%**
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%
Exposure (Including PPE options above)	Longer term systemic exposure mg/kg bw/day	**0.00297**		% of RVNAS[1]	**2.28%**
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely Toxic active Substance

Table 11: Operator exposure, Prothioconazole, Cereals, no PPE / with PPE

Substance	Prothioconazole	**Formulation** = Soluble concentrates, emulsifiable concentrate, etc.	**Application rate** = 0.156 kg a.s. /ha	**Spray dilution** = 0.78 g a.s./l	**Vapour pressure** = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer** = 2-3 m	**Number of applications** = 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral** = 100%	**Inhalation** = 100%	
RVNAS[1] (AOEL)	0.2 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	

Operator Model	Mixing, loading and application AOEM				
Potential exposure	Longer term systemic exposure mg/kg bw/day	0.285		% of RVNAS[1]	92.3%
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%
Mixing and Loading	**Gloves = Yes**	Clothing = Work wear - arms, body and legs covered		PPE = None	Soluble bags = No
Application	**Gloves = Yes**	Clothing = Work wear - arms, body and legs covered		PPE = None	Closed cabin = No
Exposure (Workwear)	Longer term systemic exposure mg/kg bw/day	**0.115**		% of RVNAS[1]	**57.5%**
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%
Exposure (Including PPE options above)	Longer term systemic exposure mg/kg bw/day	**0.00508**		% of RVNAS[1]	**2.54%**
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely Toxic active Substance

Table 12: Operator exposure, PTZ-Desthio, Cereals, no PPE / with PPE

Substance	PTZ-Desthio	**Formulation** = Soluble concentrates, emulsifiable concentrate, etc.	**Application rate** = 0.141 kg a.s. /ha	**Spray dilution** = 0.705 g a.s./l	**Vapour pressure** = low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer** = 2-3 m	**Number of applications** = 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = - %	**Dermal for in use dilution** = 44%	**Oral** = 100%	**Inhalation** = 100%	
RVNAS[1] (AOEL)	0.01 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	

Operator Model	Mixing, loading and application AOEM				
Potential exposure	Longer term systemic exposure mg/kg bw/day	M0124		% of RVNAS[1]	124%
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%
Mixing and Loading	**Gloves = Yes**	Clothing = Work wear - arms, body and legs covered		PPE = None	Soluble bags = No
Application	**Gloves = Yes**	Clothing = Work wear - arms, body and legs covered		PPE = None	Closed cabin = No
Exposure (Workwear)	Longer term systemic exposure mg/kg bw/day	**0.00817**		% of RVNAS[1]	**81.7%**
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%
Exposure (Including PPE options above)	Longer term systemic exposure mg/kg bw/day	**0.00138**		% of RVNAS[1]	**13.8%**
	Acute systemic exposure mg/kg bw/day	-		% of RVAAS[2]	-%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely Toxic active Substance

Calculations for Prothioconazole-desthio and Prothioconazole based on measurements of exposure

Estimation of systemic operator exposure

In the following systemic exposure of operators to prothioconazole and prothioconazole-desthio is estimated using the data of three field studies presented in Appendix 4.1. The algorithms applied are according to the new EFSA guidance.

Basically the estimation can follow two different approaches:

a) Systemic exposure is calculated for each operator individually using his individual exposure data and body weight and from this data set the relevant percentiles are derived;
b) Relevant percentiles are derived from the normalized exposure data for actual dermal and inhalation exposure (in mg/kg a.s.). Systemic exposure is calculated by applying the dermal absorption value to the relevant dermal exposure figure and adding inhalation exposure. For the parameters 'application rate', 'treated area' and 'body weight' standard default values are used.

With regard to dermal exposure only actual dermal exposure data are used as this reflects the real conditions while potential dermal exposure corresponds to an operator wearing nothing (= naked).

A) Estimation according to individual data

The following assumptions are made:

Operator body weight:	individual body weight of the operators
Dermal absorption	
Prothioconazole:	70%
Prothioconazole-desthio:	44%
Inhalation absorption	
Prothioconazole:	100%
Prothioconazole-desthio:	100%

The calculation of the systemic exposure is performed according to the following equation:

Systemic exposure [mg/kg bw/day] = (ADE x DA) + IE

ADE = Actual dermal exposure [mg/kg body weight]

IE = Inhalation exposure [mg/kg body weight]

DA = Dermal absorption [%]

B Exposure to prothioconazole [mg/kg bw/day]

Operator ID	Prothioconazole [mg/kg bw]		Systemic exposure to prothioconazole [mg/kg bw]	
	ADE	IE	actual*	% of AOEL
A1	0.0008947	0.0000876	0.000714	0.36
B1	0.0010625	0.0001059	0.000850	0.42
C1	0.0011806	0.0001156	0.000942	0.47
B2	0.0010625	0.0001040	0.000848	0.42
C2	0.0012139	0.0001156	0.000965	0.48
A3	0.0009474	0.0000438	0.000707	0.35
C3	0.0012611	0.0000578	0.000941	0.47
B3	0.0011250	0.0000520	0.000840	0.42
A	0.0037187	0.0000661	0.002669	1.33
B	0.0009500	0.0000208	0.000686	0.34
C	0.0011765	0.0000489	0.000872	0.44
D	0.0011765	0.0000245	0.000848	0.42
E	0.0005625	0.0000260	0.000420	0.21
A	0.0012902	0.0000507	0.000954	0.48
B	0.0005455	0.0000378	0.000420	0.21
C	0.0007992	0.0000353	0.000595	0.30
D	0.0010714	0.0000495	0.000799	0.40
E	0.0004442	0.0000438	0.000355	0.18
F	0.0004839	0.0000447	0.000383	0.19
H	0.0003833	0.0000347	0.000303	0.15

ADE = actual dermal exposure, IE = inhalation exposure
*actual systemic exposure corresponds to an operator wearing work clothing, gloves during mixing/loading and when handling contaminated surfaces

C) Statistical summary

Statistical parameter	Systemic exposure to prothioconazole Work clothing and PPE	
	mg/kg bw	% of AOEL
Empirical 75th percentile	0.000889	0.44
Empirical 95th percentile	0.00105	0.53
Maximum	0.00267	1.33
Parametric 75th percentile	**0.00100**	**0.50**
Log normality	No	

D) Exposure to prothioconazole-desthio [mg/kg bw/day]

Operator ID	Prothioconazole-desthio [mg/kg bw]		Systemic exposure to prothioconazole-desthio [mg/kg bw]	
	ADE	IE	actual*	% of AOEL
A1	0.0002947	0.0000876	0.0002173	2.17
B1	0.00035	0.000104	0.000258	2.58
C1	0.0003889	0.0001156	0.0002867	2.87
B2	0.00035	0.000104	0.000258	2.58
C2	0.0003889	0.0001156	0.0002867	2.87
A3	0.0003158	0.0000938	0.0001828	1.83
C3	0.0004167	0.0000578	0.0002411	2.41
B3	0.0004513	0.000052	0.0002506	2.51
A	0.002132	0.0000277	0.0009658	9.66
B	0.000327	0.0000208	0.0001647	1.65
C	0.0004	0.0000489	0.0002249	2.25
D	0.0004	0.0000245	0.0002005	2.01
E	0.0004	0.000026	0.000202	2.02
A	0.0003902	0.0000507	0.0002224	2.22
B	0.00026	0.0000378	0.000139	1.39
C	0.0004398	0.0000353	0.0002288	2.29
D	0.0003571	0.0000495	0.0002066	2.07
E	0.0001674	0.0000438	0.0001175	1.17
F	0.000129	0.0000447	0.0001015	1.01
H	0.0001092	0.0000347	0.0000827	0.83

ADE = actual dermal exposure, IE = inhalation exposure
*actual systemic exposure corresponds to an operator wearing work clothing, gloves during mixing/loading and when handling contaminated surfaces

E) Statistical summary

Statistical parameter	Systemic exposure to prothioconazole-desthio Work clothing and PPE	
	mg/kg bw	% of AOEL
Empirical 75th percentile	0.0002524	2.52
Empirical 95th percentile	0.000321	3.21
Maximum	0.000966	9.66
Parametric 75th percentile	**0.000297**	**2.98**
Log normality	No	

Details on the studies

New additional studies have been submitted. They have been previously evaluated within the peer reviewed process at EU level for the active substance Prothioconazole. Summaries according to the peer review for Prothioconazole are presented in the following.

Operator exposure study for Prothioconazole / Prothioconazole-desthio (KCP 7.2.1.2)

It has been found that prothioconazole in diluted solutions can convert to prothioconazole-desthio (other internal code: SXX 0665) during the drying process on clothing, skin or on certain plant surfaces. The conversion product, prothioconazole-desthio is known to have an embryotoxic potential in experimental animals. Therefore, three operator exposure studies were conducted to determine the exposure to prothioconazole as well as to prothioconazole-desthio under real use conditions and thus to get a better basis for a realistic risk assessment.
The first study was already submitted and evaluated for Annex I inclusion of prothioconazole. Since then BCS has conducted two further exposure studies with twelve farmers under real and representative conditions in cereals and canola (one application).

All operator exposure studies have been (re-)evaluated during the AIR process for PTZ. For details please refer to the draft renewal assessment report for PTZ, which is publicly available on the EFSA webpage[2]. For the sake of transparency and value traceability the study evaluation procedure described in this chapter follows the approach taken during the re-evaluation, even though the applicant disagrees with some evaluation points:

- **Values lower than the LoQ have been reported at the LoQ instead of 1/2 LoQ**
- **Recoveries < 95% were already corrected instead of following the approach from the AOEM (correction when < 70%)**

The studies are also part of the new AOEModel (EFSA Model for operator exposure). However, as the studies were set up as mixer/loader/applicator studies only part of the data are used in the model. In addition, the data in the model are used as prothioconazole-equivalents (sum of exposures to prothioconazole and prothioconazole-desthio) and, hence, do not allow to distinguish between exposure to prothioconazole and prothioconazole-desthio.

Therefore, it is reasonable to make use of the compound and crop specific study data as higher tier for the assessment of exposure to prothioconazole and prothioconazole-desthio.

For Annex I renewal of prothioconazole all studies are referenced again and are evaluated according to the new EFSA guidance.

[2] EFSA: Public consultation on the active substance prothioconazole: https://www.efsa.europa.eu/de/consultations/call/180612

Comments of zRMS:	Comment on study; acceptable or not; deficiencies, corrections, according to recent guidelines or not, used in evaluation or only as additional information .

Data Point:	KCP 7.2.1.2/01
Report Author:	[redacted]
Report Year:	2002
Report Title:	Determination of exposure to JAU 6476 and JAU 6476-desthio (SXX 0665) during mixing/loading and application of JAU 6476 in cereals
Report No:	MR-036/02
Document No:	M-040604-01-2
Guideline(s) followed in study:	not specified
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I Materials and methods

The study was designed as a mixer/loader/applicator-study. In addition to the determination of exposure to prothioconazole the proportion of conversion to prothioconazole-desthio and the resulting exposure to prothioconazole-desthio was determined.
A total of eight applications at three different spray timings involving three different male operators were monitored. The operators were employees of Bayer AG (now: Bayer CropScience) and were familiar with the practice of mixing/loading and application of plant protection products. All applications were performed during the actual season (May/June 2000) on a field belonging to an agricultural test site of Bayer AG (now: Bayer CropScience) in Monheim (Germany). With each application about 20 ha were treated using spray equipment that was appropriate and representative (tractor drawn/mounted ground boom sprayer). During the first two spray timings equipment for larger field sizes was used (28 m boom, 2500 L water tank volume) whereas during the third spray timing an equipment for smaller field sizes was chosen (15 m boom, 800 L water tank volume). The tractors used were all equipped with a cabin.
Dermal exposure of the body was determined via whole body underwear (long sleeved T-shirt, long johns) as well as by analyzing a cotton shirt and a pair of trousers (cotton/polyester) as outer garments. Exposure to the head was determined by a cap. The results of the outer garments and the cap together with the results of the underwear correspond to potential dermal exposure of the body whereas the results of the underwear plus the cap are regarded as actual dermal body exposure when wearing only one layer of clothing.
Hand exposure was determined via glove rinsing and hand washing. The results of the glove rinsing together with the hand washing correspond to potential hand exposure whereas the results of the hand washing are regarded as actual hand exposure. According to usual agricultural practice protective gloves were always worn during mixing/loading whereas during application gloves had only been worn if the operator had to handle contaminated surfaces, e.g. correcting a machine malfunction.
Inhalation exposure was measured via IOM-samplers equipped with glass fiber filters which were fixed to the garments at the breathing zone of the operator and connected to a personal powered air pump.
Field recovery samples to assess the stability of prothioconazole and prothioconazole-desthio were performed on all sampling media exposed appropriately on each spraying occasion.
The spraying lasted between 2.5 h and 3.5 h. On completion of the spraying the cap and the gloves were sampled and also a hand wash was performed. The operators continued to wear the other dosimeter clothes for some further hours to give a total of about 7 h (one exception: ca. 5.2 h) to provide some information on the proportion of conversion of prothioconazole to prothioconazole-desthio during the time of almost a full work day.

Samples were extracted, followed by LC-MS/MS determination. In the report the results of the measurements are reported as determined (i.e., µg a.s. per sample) and as specific (normalized) exposures, i.e., as mg of exposure per kg of a.s. handled.

II Results and discussion

The limit of quantitation (LOQ) per sample was 50 µg (outer garments), 10 µg (undergarments) and 5 µg (hand wash water) for prothioconazole and 20 µg, 2 µg and 2 µg for prothioconazole-desthio, respectively. For samples which showed results <LOQ the exposure values for prothioconazole and prothioconazole-desthio were then calculated from figures corresponding to half of the LOQ.
Prothioconazole-equivalents can be calculated in summing up the exposure figures for prothioconazole and prothioconazole-desthio, calculated as prothioconazole by taking into account the molar ratio.
The exposure figures for each operator expressed as dermal exposures to prothioconazole and to prothioconazole-desthio in mg as well as in mg/kg body weight and mg/kg prothioconazole handled are listed in the Tables below. Potential dermal exposure comprises all dermal sampling items, i.e., outer clothing, cap, undergarments, gloves rinsings and hand washes. Actual dermal exposure comprises cap, undergarments and hand washes.
On eight samples of the outer clothing measurable amounts of prothioconazole were found, in four of these samples and in one additional sample also prothioconazole-desthio could be quantified (out of a total of 32 samples). The percentage of conversion with respect to total "prothioconazole-equivalents" was found to be very variable, ranging from 3% to nearly 50%.
Also on gloves and in some of the hand wash solutions prothioconazole and prothioconazole-desthio were found. The corresponding percentages of prothioconazole-desthio to total "prothioconazole equivalents" cover the range from 1% to 60%.
With regard to inhalation exposure only prothioconazole was found and only in two filters. For both samples the amount of prothioconazole was at the level of LOQ (0.1 µg/sample).
Spray tank samples which were also analyzed showed that prothioconazole-desthio amounted from 0.1% up to about maximum 1% of total "prothioconazole-equivalents", with a mean of 0.22%.

Table 13: Summary of prothioconazole residues found in each sampling dosimeter (corrected for field recoveries)

Operator ID	A1	B1	C1	B2	C2	A3	C3	B3
Body weight (kg)	95	80	72	80	72	95	72	80
Area treated (≈ha)	20	20	20	20	20	20	20	20
Exposure time (minutes)	206	160	174	165	155	208	198	202
Prothioconazole handled (kg)	3.96	4.03	4.03	4.03	4.03	4.06	4.06	4.06
Outer clothing (µg prothioconazole / sample)								
Sleeves (cotton)	50	50	50	50	810	356	50	50
Shirt torso (cotton)	189	50	50	50	50	50	50	50
Trousers torso (cotton/polyester)	203	50	82	50	50	50	82	50
Legs (cotton/polyester)	50	50	50	50	50	334	94	50
Total outer clothing	493	200	237	200	960	791	276	200
Inner clothing (µg prothioconazole / sample)								
Sleeves	10	10	10	10	10	10	10	10
Torso	10	10	10	10	10	10	10	10
Legs	10	10	10	10	10	10	10	10
Total inner clothing	30	30	30	30	30	30	30	30
Cap (µg prothioconazole / sample)								
Cap	50	50	50	50	50	50	50	50
Hand wash (µg / sample)								
Hand washings in esemtan	5	5	5	5	7.4	5	5.8	5
Hand washings in isopropanol			-	-	-	5	5	5
Total hand	5	5	5	5	7.4	10	10.8	10
Nitrile gloves rinsing (µg prothioconazole / sample)								
Total gloves	2319	6561	4917	2278	19861	15000	29722	19306
Air filter (µg prothioconazole / sample)								
1st mixing/loading filter	0	0.1	0.1	0.1	0.1	0.1	0.1	0.1
1st mixing/loading cassette	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
1st application filter	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
1st application cassette	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
2nd mixing/loading filter	0.1	0.1	0.1	0.1	0.1	-	-	-
2nd mixing/loading cassette	0.1	0.1	0.1	0.1	0.1	-	-	-
2nd application filter	0.1	0.1	0.1	0.1	0.1	-	-	-
2nd application cassette	0.1	0.1	0.1	0.1	0.1	-	-	-
Total inhalation dosimeters	0.8	0.8	0.8	0.8	0.8	0.4	0.4	0.4

Values in red are <LOQ and have been reported at the LOQ	
(-) no sample taken	
	values corrected for 48% field recovery (applicable to the 125 ug/sample spiking level with diluted formulation for cotton outer garments for prothioconazole)
	values corrected for 55% field recovery (applicable to the 100 ug/sample spiking level with diluted formulation for cotton outer garments for prothioconazole)
	values corrected for 58% field recovery (applicable to the 125 µg/sample spiking level for cotton polyester outer garments for prothioconazole)
	values corrected for 62% field recovery (applicable to the 100 µg/sample spiking level for cotton/polyester outer garments for prothioconazole)
	values corrected for 72% recovery (applicable to the 3000 ng/sample for gloves for prothioconazole)
	values corrected for 87% recovery (applicable to the 0.2 µg/sample for glass fibre filters with cysteine)

Table 14: Summary of estimated systemic exposure to prothioconazole

Operator ID	A1	B1	C1	B2	C2	A3	C3	B3
Body weight (kg)	95	80	72	80	72	95	72	80
Outer clothing (mg)	0.4925	0.2000	0.2351	0.2000	0.9604	0.7907	0.2758	0.2000
Inner clothing (mg)	0.0300	0.0300	0.0300	0.0300	0.0300	0.0300	0.0300	0.0300
Head (mg)	0.0500	0.0500	0.0500	0.0500	0.0500	0.0500	0.0500	0.0500
Hands(mg)	0.0050	0.0050	0.0050	0.0050	0.0074	0.0100	0.0108	0.0100
Nitrile gloves (mg)	7.3194	6.8611	4.9167	2.2778	10.8611	15.0000	29.7222	19.3056
Air sampler (mg)	0.0008	0.000815	0.0008	0.0008	0.0008	0.0004	0.0004	0.0004
PDE_{body} (mg/person)	0.9725	0.2800	0.3171	0.2800	1.0404	0.8707	0.3558	0.2800
PDE_{hands} (mg/person)	2.3243	6.8661	4.9267	2.2828	19.8685	15.0100	29.7330	19.3156
ADE_{body} (mg/person)	0.0800	0.0800	0.0800	0.0800	0.0800	0.0800	0.0800	0.0800
ADE_{hands} (mg/person)	0.0050	0.0050	0.0050	0.0050	0.0074	0.0100	0.0108	0.0100
PIE (mg/person)	0.00832	0.00847	0.00832	0.00832	0.00832	0.00416	0.00416	0.00416
PDE (mg/person)	2.89690	7.14610	5.23880	2.56280	20.90890	15.88070	30.08880	19.59560
ADE (mg/person)	0.08500	0.08500	0.08500	0.08500	0.08740	0.09000	0.09080	0.09000
PIE (mg/kg)	0.00009	0.00011	0.00012	0.00010	0.00012	0.00004	0.00006	0.00005
PDE (mg/kg)	0.03049	0.08933	0.07276	0.03204	0.29040	0.16717	0.41790	0.24495
ADE (mg/kg)	0.00089	0.00106	0.00118	0.00106	0.00121	0.00095	0.00126	0.00113

PIE= Potential inhalation exposure,

PDE=Potential Dermal Exposure (naked),

ADE=Actual dermal exposure (one layer of clothing + gloves during mixing and loading and when handling contaminated surfaces)

Table 15: Summary of prothioconazole-desthio residues found in each sampling dosimeter (corrected for field recoveries)

Operator number	A1	B1	C1	B2	C2	A3	C3	B3
Body weight (kg)	95	80	72	80	72	95	72	80
Area treated (≈ha)	20	20	20	20	20	20	20	20
Exposure time (mins)	206	160	174	165	155	208	198	202
Prothioconazole handled (kg)	3.96	4.03	4.03	4.03	4.03	4.06	4.06	4.06
Outer clothing (µg prothioconazole-desthio/sample)								
Sleeves (cotton)	20	20	20	20	20	23	20	20
Shirt torso (cotton)	20	20	20	20	20	20	20	20
Trousers torso (cotton/polyester)	45	20	20	20	20	20	20	20
Legs (cotton/polyester)	20	20	20	20	20	30	21	20
TOTAL	105	80	80	80	80	93	81	80
Inner clothing (µg prothioconazole-desthio/sample)								
Sleeves	2	2	2	2	2	2	2	2
Torso	2	2	2	2	2	2	2	2
Legs	2	2	2	2	2	2	2	2
TOTAL	6	6	6	6	6	6	6	6
Cap (µg prothioconazole-desthio/sample)								
TOTAL	20	20	20	20	20	20	20	20

Handwash (µg prothioconazole-desthio/sample)								
Hand washings in esemtan	2	2	2	2	2	2	2	5.1
Hand washings in isopropanol	-	-	-	-	-	2	2	5
TOTAL	2	2	2	2	2	4	4	10.1
Nitrile gloves rinsings (µg prothioconazole-desthio/sample)								
Nitrile gloves rinsings	33	103	88	255	606	2522	4183	3411
Air filter (µg prothioconazole-desthio/sample)								
Mixing/loading 1 filter	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Mixing/loading 1 cassette	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Application 1 filter	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Application 1 cassette	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Mixing/loading 2 filter	0.1	0.1	0.1	0.1	0.1	-	-	-
Mixing/loading 2 cassette	0.1	0.1	0.1	0.1	0.1	-	-	-
Application 2 filter	0.1	0.1	0.1	0.1	0.1	-	-	-
Application 2 cassette	0.1	0.1	0.1	0.1	0.1	-	-	-
TOTAL	0.8	0.8	0.8	0.8	0.8	0.4	0.4	0.4
Values in red are <LOQ and have been reported at the LOQ								
	values corrected for 23% field recovery (applicable to the 50 ug/sample spiking level for gloves)							
	values corrected for 18% field recovery (applicable to the 500 ug/sample spiking level for gloves)							

Table 16: Summary of estimated systemic exposure to prothioconazole-desthio

Operator ID	A1	B1	C1	B2	C2	A3	C3	B3
Bodyweight (kg)	95	80	72	80	72	95	72	80
Outer clothing (mg)	0.1050	0.0800	0.0800	0.0800	0.0800	0.0930	0.0810	0.0800
Inner clothing (mg)	0.0060	0.0060	0.0060	0.0060	0.0060	0.0060	0.0060	0.0060
Head (mg)	0.0200	0.0200	0.0200	0.0200	0.0200	0.0200	0.0200	0.0200
Hands (mg)	0.0020	0.0020	0.0020	0.0020	0.0020	0.0040	0.0040	0.0101
Nitrile gloves (mg)	0.0333	0.1030	0.0879	0.2545	0.6061	2.6022	4.1833	3.4111
Air sampler (mg)	0.0008	0.0008	0.0008	0.0008	0.0008	0.0004	0.0004	0.0004
PDE_{body} (mg/person)	0.1310	0.1060	0.1060	0.1060	0.1060	0.1190	0.1070	0.1060
PDE_{hands} (mg/person)	0.0353	0.1050	0.0899	0.2565	0.6081	2.5262	4.1873	3.4212
ADE_{body} (mg/person)	0.0260	0.0260	0.0260	0.0260	0.0260	0.0260	0.0260	0.0260
ADE_{hands} (mg/person)	0.0020	0.0020	0.0020	0.0020	0.0020	0.0040	0.0040	0.0101
PIE (mg/person)	0.00832	0.00832	0.00832	0.00832	0.00832	0.00416	0.00416	0.00416
PDE (mg/person)	0.16630	0.21100	0.19590	0.36250	0.71410	2.64520	4.29430	3.52720
ADE (mg/person)	0.02800	0.02800	0.02800	0.02800	0.02800	0.03000	0.03000	0.03610
PIE (mg/kg)	0.00009	0.00010	0.00012	0.00010	0.00012	0.00004	0.00006	0.00005
PDE (mg/kg)	0.00175	0.00264	0.00272	0.00453	0.00992	0.02784	0.05964	0.04409
ADE (mg/kg)	0.00029	0.00035	0.00039	0.00035	0.00039	0.00032	0.00042	0.00045

PIE= Potential inhalation exposure,
PDE=Potential Dermal Exposure (naked),
ADE=Actual dermal exposure (one layer of clothing + gloves during mixing and loading and when handling contaminated surfaces)

III Conclusion

A final conclusion of all study results is given under "overall summary and conclusions".

Comments of zRMS:	Comment on study: acceptable or not; deficiencies, corrections, according to recent guidelines or not, used in evaluation or only as additional information

Data Point:	KCP 7.2.1.2/02
Report Author:	[redacted]
Report Year:	2015
Report Title:	Determination of exposure during mixing/loading and application of Proline in cereals
Report No:	MR-156/05
Document No:	M-285798-02-1
Guideline(s) followed in study:	not specified
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I Materials and methods

The study was designed as a mixer/loader/applicator-study. In addition to the determination of exposure to prothioconazole the proportion of conversion to prothioconazole-desthio and the resulting exposure to prothioconazole-desthio was determined.
A total of five applications involving five different male operators were monitored. The operators were independent farmers and were familiar with the practice of mixing/loading and application of plant protection products. All applications were performed during May to June 2005 on fields in the surroundings of Limburg, Büdingen and Darmstadt (Germany). The areas treated ranged from 19 ha to 67 ha. Each of the operators performed a day's work according to his average usual working practice. Three operators used equipment for smaller field sizes (15 m boom, 1000 L water tank volume) whereas in two cases equipment for larger sizes was used (18/30 m boom, 3000/4000 L water tank volume). The tractors used were all equipped with a cabin. However, depending on the weather and the equipment some operators left the back and/or front window open as well as the roof opening. Dermal exposure of the body was determined via whole body underwear (long sleeved T-shirt, long johns) as well as by analyzing a cotton shirt and a pair of trousers (cotton/polyester) as outer garments. Exposure to the head was determined by a cap. The results of the outer garments and the cap together with the results of the underwear correspond to potential dermal exposure of the body whereas the results of the underwear plus the cap are regarded as actual dermal exposure when wearing only one layer of clothing.
The operators were not forced to wear a cap if this was not in accordance to their normal working clothes and behavior. One operator made use of this option.
Hand exposure was determined via glove rinsing and hand washing. The results of the glove rinsing together with the hand washing correspond to potential hand exposure whereas the results of the hand washing are regarded as actual hand exposure. According to usual agricultural practice protective gloves were always worn during/mixing loading whereas during application gloves were only worn in case the operator had to handle contaminated surfaces, e.g. un-/folding the boom manually or correcting a machine malfunction like blocked or lost nozzles.
If operators took off their outer clothes during a break they received Kleenguard suits to be worn above the inner dosimeters. Afterwards, the Kleenguard suits were sampled as a whole.
One incident occurred during a mixing/loading cycle of one operator: as he was not accustomed yet to a new water supply system the tank ran over and he got splashes of spray liquid on his clothes. He received a second set of clothing but all data are included in his overall exposure evaluation.
Inhalation exposure was measured via IOM-samplers equipped with glass fiber filters which were fixed to the garments at the breathing zone of the operator and connected to a personal powered air pump.
Field recoveries were set up at two sites. All sampling media were used and exposed appropriately.
The monitoring lasted between 5 h and 8 h, corresponding to a normal full work day. On completion of the last spraying all dosimeters were sampled and also a hand wash was performed.

Samples were extracted, followed by LC-MS/MS determination. In the report the results of the measurements are reported as determined (i.e., µg a.s. per sample) and as specific (normalized) exposures, i.e., as mg of exposure per kg of a.s. handled.

II Results and discussion

The limit of quantitation (LOQ) per sample was 50 µg (outer garments), 10 µg (undergarments) and 5 µg (hand wash water) for prothioconazole and 20 µg, 2 µg and 2 µg for prothioconazole-desthio, respectively. For samples which showed results <LOQ the exposure values for prothioconazole and prothioconazole-desthio were then calculated from figures corresponding to half of the LOQ. Prothioconazole-equivalents can be calculated in summing up the exposure figures for prothioconazole and prothioconazole-desthio, calculated as prothioconazole by taking into account the molar ratio. The exposure figures for each operator expressed as dermal exposures to prothioconazole and to prothioconazole-desthio in mg as well as in mg/kg body weight and mg/kg prothioconazole handled are listed in the Tables below. Potential dermal exposure comprises all dermal sampling items, i.e., outer clothing, cap, undergarments, gloves rinsings and hand washes. Actual dermal exposure comprises cap, undergarments and hand washes.

Table 17: Summary of prothioconazole residues found in each sampling dosimeter (corrected for field recoveries)

Operator ID	A	B	C	D	E
Body weight (kg)	75	100	85	85	80
Area treated (≈ha)	67.4	18.9	32.8	48.8	25.9
Exposure time (minutes)	352	294	381	403	183
Prothioconazole handled (kg)	14	4	7	10.1	5.3
Prothioconazole applied (kg)	13.6	4	6	10.8	5.3
Outer dosimeter (µg prothioconazole/ sample)					
Sleeves	171	50	50	50	52
Shirt torso	78	50	50	59	50
Trousers torso	548	50	969	50	64
Legs	753	83	925	50	50
Total outer dosimeters	1550	233	1994	209	216
Inner dosimeter (µg prothioconazole/ sample)					
Sleeves	10	10	10	10	10
Torso	10	10	10	10	10
Legs	10	10	10	10	10
Total inner dosimeters	30	30	30	30	30
Cap (µg prothioconazole/ sample)					
Total	50	50	50	50	-
Hand wash (µg prothioconazole/ sample)					
Hand washings in esemtan*	194	10	15	15	10
Hand washings in isopropanol	5	5	5	5	5
Total hand wash	199	15	20	20	15
Nitrile gloves rinsings (µg prothioconazole/ sample)					
Nitrile gloves rinsings (neat)	13714	3943	9986	887	2157
Nitrile gloves rinsings (application)	5	1309	-	706	-
Total gloves	13719	5251	9986	1593	2157
Air filter (µg prothioconazole/ sample)					
1st Mixing/loading	0.3	0.1	0.1	0.1	0.1
1st Application	0.2	0.1	0.1	0.1	0.1
2nd Mixing/loading	-	-	0.1	-	-
2nd Application	-	-	0.1	-	-
Total inhalation dosimeters	0.5	0.2	0.4	0.2	0.2

Values in red are < LOQ and have been reported at the LOQ

(-) no sample taken

* During the study a number of hand wash samples in esemtam were taken. If multiply samples were < LOQ, these have been summed together assuming each sample was at the LOQ (e.g. if there are 3 samples < LOQ, these have been reported at 3 x LOQ (i.e. 15 µg)

	Values corrected for 66% recovery (applicable to the 0.04 µg/mL spiking level for hand wash)
	Values corrected for 70% recovery (applicable to the 10000 µg/sample spiking level for nitrile gloves)
	Values corrected for 65% recovery (applicable to the 0.2 µg/sample spiking level for glass fibre filters)

Table 18: Summary of estimated systemic exposure to prothioconazole

Operator	A	B	C	D	E
Bodyweight (kg)	75	100	85	85	80
Outer clothing (mg)	1.5500	0.2330	1.9940	0.2090	0.2160
Inner clothing (mg)	0.0300	0.0300	0.0300	0.0300	0.0300
Head (mg)	0.0500	0.0500	0.0500	0.0500	-
Hands (mg)	0.1989	0.0150	0.0200	0.0200	0.0150
Nitrile gloves (mg)	13.7193	5.2514	9.9857	1.5929	2.1571
Air sampler (mg)	0.00048	0.0002	0.0004	0.0002	0.0003
PDE_{body} (mg/person)	1.6300	0.3130	2.0740	0.2890	0.2460
PDE_{hands} (mg/person)	13.9182	5.2664	10.0057	1.6129	2.1721
ADE_{body} (mg/person)	0.0800	0.0800	0.0800	0.0800	0.0300
ADE_{hands} (mg/person)	0.1989	0.0150	0.0200	0.0200	0.0150
PIE (mg/person)	0.00496	0.00208	0.00416	0.00208	0.0020 8
PDE (mg/person)	0.00496	0.00208	0.00416	0.00208	0.00208
ADE (mg/person)	15.54820	5.57940	12.07970	1.90190	2.41810
PIE (mg/kg)	0.27890	0.09500	0.10000	0.10000	0.04500
PDE (mg/kg)	0.00007	0.00002	0.00005	0.00002	0.00003
ADE (mg/kg)	0.20731	0.0529	0.14211	0.02238	0.03023

PIE= Potential inhalation exposure;
PDE=Potential Dermal Exposure (naked);
ADE=Actual dermal exposure (one layer of clothing + gloves during mixing and loading and when handling contaminated surfaces)

Table 19: Summary of prothioconazole-desthio residues found in each sampling dosimeter (corrected for field recoveries)

Operator number	A	B	C	D	E
Body weight (kg)	75	100	85	85	80
Area treated (ha)	67.4	18.9	32.8	48.8	25.2
Exposure time (mins)	352	294	381	403	483
Prothioconazole handled (kg)	14	4	7	13.1	5.3
Prothioconazole applied (kg)	3.96	4.03	4.03	4.03	4.03
Outer dosimeter (µg prothioconazole-desthio/ sample)					
Sleeves	88	20	20	20	20
Shirt torso	50	20	20	20	20
Trousers torso	120	20	128	20	20
Legs	214	42	45	29	20
Total outer dosimeters	472	102	213	89	80
Inner dosimeter (µg prothioconazole-desthio/ sample)					
Sleeves	2	2	2	2	2
Torso	2.7	2	2	2	2
Legs	2	2	2	2	2
Total inner dosimeters	6.7	6	6	6	6
Cap (µg prothioconazole-desthio/ sample)					
TOTAL	20	20	20	20	-
Handwash (µg prothioconazole-desthio/ sample)					
Hand washings in esemtan*	129	5	6	6	4
Hand washings in isopropanol	4	2	2	2	2
Total hand washings	133	7	8	8	6
Nitrile gloves rinsings (µg prothioconazole- desthio/ sample)					
Nitrile gloves rinsings (m/l)	731	286	597	65	95
Nitrile gloves rinsings (application)	2	116	-	115	-
Total gloves	733	402	597	180	95
Air filter (µg prothioconazole- desthio/ sample)					
1st Mixing/loading	0.1	0.1	0.1	0.1	0.1
1st Application	0.1	0.1	0.1	0.1	0.1
2nd Mixing/loading	-	-	0.1	-	-
2nd Application	-	-	0.1	-	-
Total inhalation dosimeters	0.2	0.2	0.4	0.2	0.2
Values in red are <LOQ and have been reported at the LOQ					
(-) no sample taken					
** During the study a number of hand wash samples in esemtam were taken. If multiple samples were < LOQ, these have been summed together assuming each sample was at the LOQ (e.g. if there are 3 samples < LOQ, these have been reported at 3 x LOQ (i.e. 15 µg)					
[pink shading]	values corrected for 92% recovery (applicable to the 0.04 ug/mL spiking level for hand wash)				
[beige shading]	values corrected for 86% recovery (applicable to the 3000 µg/sample spiking level for gloves)				

Table 20: Summary of estimated systemic exposure to prothioconazole-desthio

Operator	A	B	C	D	E
Bodyweight (kg)	75	100	85	85	80
Outer clothing (mg)	0.4720	0.1020	0.2130	0.0890	0.0800
Inner clothing (mg)	0.0067	0.0060	0.0060	0.0060	0.0060
Head (mg)	0.0200	0.0200	0.0200	0.0200	0.0200
Hands (mg)	0.1332	0.0067	0.0080	0.0080	0.0060
Nitrile gloves (mg)	0.7314	0.2860	0.5965	0.0651	0.0953
Air sampler (mg)	0.0002	0.0002	0.0004	0.0002	0.0002
PDE_{body} (mg/person)	0.4987	0.1280	0.2390	0.1150	0.1060
PDE_{hands} (mg/person)	0.8645	0.2927	0.6045	0.0731	0.1013
ADE_{body} (mg/person)	0.0267	0.0260	0.0260	0.0260	0.0260
ADE_{hands} (mg/person)	0.1332	0.0067	0.0080	0.0080	0.0060
PIE (mg/person)	0.00208	0.00208	0.00416	0.00208	0.00208
PDE (mg/person)	1.36320	0.42070	0.84350	0.18810	0.20730
ADE (mg/person)	0.15990	0.03270	0.03400	0.03400	0.03200
PIE (mg/kg)	0.00003	0.00002	0.00002	0.00002	0.00003
PDE (mg/kg)	0.01818	0.00421	0.00992	0.00221	0.00259
ADE (mg/kg)	0.00213	0.00033	0.00040	0.00040	0.00040

PIE= Potential inhalation exposure;

PDE=Potential Dermal Exposure (naked);

ADE=Actual dermal exposure (one layer of clothing + gloves during mixing and loading and when handling contaminated surfaces)

On 12 samples of the outer clothing measurable amounts of prothioconazole were found; in eight of these samples and in one additional sample also prothioconazole-desthio could be quantified (out of a total of 24 samples). The percentage of conversion with respect to total "prothioconazole-equivalents" was found to be very variable, ranging from 5% to 56%. Also on gloves and in some of the hand wash solutions prothioconazole and prothioconazole-desthio were found. The corresponding percentages of prothioconazole-desthio to total "prothioconazole equivalents" cover the range from 3% to 60%.

With regard to inhalation exposure only prothioconazole was found and only in two filters (of one operator). For both samples the amount of prothioconazole was at the level of LOQ.

III Conclusion

A final conclusion of all spray application results are given under "overall summary and conclusions".

Comments of zRMS:	Comment on study; acceptable or not; deficiencies, corrections, according to recent guidelines or not, used in evaluation or only as additional information .

Data Point:	KCP 7.2.1.2/03
Report Author:	[redacted]
Report Year:	2007
Report Title:	Determination of exposure during mixing/loading and application of prothioconazole in cereals and canola
Report No:	MR-244/07
Document No:	M-286545-01-1
Guideline(s) followed in study:	not specified
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

I Materials and methods

The study was designed as a mixer/loader/applicator-study. In addition to the determination of exposure to prothioconazole the proportion of conversion to prothioconazole-desthio and the resulting exposure to prothioconazole-desthio was determined.

A total of seven applications involving seven different male operators were monitored. The operators were independent farmers or employees of a farm cooperative. They were familiar with the practice of mixing/loading and application of plant protection products. All applications were performed during May to June 2006 on fields in the surroundings of Weimar/Gera and Swisttal/Weilerswist (Germany). The areas treated ranged from 23 ha to 180 ha. Each of the operators performed a day's work or at least 5 hours according to his average usual working practice. Three operators used equipment for smaller field sizes (15/21 m boom, 840 - 1500 L water tank volume) whereas in four cases equipment for larger sizes was used (24/36 m boom, 2600/4000 L water tank volume). The tractors used were all equipped with a cabin. However, depending on the weather and the equipment some operators left the back and/or front window open as well as the roof opening.

Dermal exposure of the body was determined via whole body underwear (long sleeved T-shirt, long johns) as well as by analyzing a cotton shirt and a pair of trousers (cotton/polyester) as outer garments. Exposure to the head was determined by a cap. The results of the outer garments and the cap together with the results of the underwear correspond to potential dermal exposure of the body whereas the results of the underwear plus the cap are regarded as actual dermal exposure when wearing only one layer of clothing.

The operators were not forced to wear a cap if this was not in accordance to their normal working clothes and behavior. Four operators made use of this option.

Hand exposure was determined via glove rinsing and hand washing. The results of the glove rinsing together with the hand washing correspond to potential hand exposure whereas the results of the hand washing are regarded as actual hand exposure. According to usual agricultural practice protective gloves were always worn during mixing loading whereas during application gloves were only worn in case the operator had to handle contaminated surfaces, e.g. un-/folding the boom manually or correcting a machine malfunction like blocked or lost nozzles.

If operators took off their outer clothes during a break they received Kleenguard suits to be worn above the inner dosimeters. Afterwards, the Kleenguard suits were sampled as a whole.

In addition to the usual spraying also the following occurrences were monitored: one operator had some blocked nozzles and brushed them off several times; another operator replaced the outer spray nozzles by blind nozzles in order to avoid spraying of the adjacent field.

Inhalation exposure was measured via IOM-samplers equipped with glass fiber filters which were fixed to the garments at the breathing zone of the operator and connected to a personal powered air pump.

Field recoveries were set up at one site. All sampling media were used and exposed appropriately.
The whole monitoring lasted between 5 h and 9 h. On completion of the last spraying all dosimeters were sampled and also a hand wash was performed.
Samples were extracted, followed by LC-MS/MS determination. In the report the results of the measurements are reported as determined (i.e., µg a.s. per sample) and as specific (normalized) exposures, i.e., as mg of exposure per kg of a.s. handled.

II Results and discussion

The limit of quantitation (LOQ) per sample was 50 µg (outer garments), 10 µg (undergarments) and 5 µg (hand wash water) for prothioconazole and 20 µg, 2 µg and 2 µg for prothioconazole-desthio, respectively. For samples which showed results <LOQ the exposure values for prothioconazole and prothioconazole-desthio were then calculated from figures corresponding to half of the LOQ.
Prothioconazole-equivalents can be calculated in summing up the exposure figures for prothioconazole and prothioconazole-desthio, calculated as prothioconazole by taking into account the molar ratio.
The exposure figures for each operator expressed as dermal exposures to prothioconazole and to prothioconazole-desthio in mg as well as in mg/kg body weight and mg/kg prothioconazole handled are listed in the Tables below. Potential dermal exposure comprises all dermal sampling items, i.e., outer clothing, cap, undergarments, gloves rinsings and hand washes. Actual dermal exposure comprises cap, undergarments and hand washes.

Table 21: Summary of prothioconazole residues found in each sampling dosimeter (corrected for field recoveries)

Operator ID	A	B	C	D	E	F	H
Body weight (kg)	82	110	118	84	95	93	120
Area treated (≈ha)	23	64	180	60	30.3	35	80
Exposure time (mins)	427	317	515	287	520	457	350
Prothioconazole handled (kg)	4.6	12.8	31.3	12	5.6	7.1	15
Prothioconazole applied (kg)	4.6	12.8	31.3	12	5.6	6.9	15
Outer clothing (µg prothioconazole/ sample)							
Sleeves	54	183	1160	50	445	89	2720
Shirt torso	50	92	170	50	55	50	448
Trousers torso	50	50	1360	50	50	50	50
Legs	56	59	2190	65	331	159	186
Total outer clothing	210	384	4880	215	881	348	3404
Inner clothing (µg prothioconazole/ sample)							
Sleeves	19	10	10	10	10	10	16
Torso	10	10	12	10	10	10	10
Legs	10	10	10	10	10	10	10
Total inner clothing	39	30	32	30	30	30	36
Cap (µg prothioconazole/ sample)							
Total head	50	-	50	50	-	-	-
Hand wash (µg prothioconazole/ sample)							
Hand washings in esemtan*	11	25	5.1	5	7.5	10	5
Hand washings in isopropanol	6.3	5	7.2	5	5	5	5
Total hand washing	17	30	12	10	12	15	10
Nitrile gloves rinsings (µg prothioconazole/ sample)							
Nitrile gloves rinsings (mL)	3718	9120	3482	568	1600	6965	3882
Nitrile gloves rinsings (application)	400	-	-	-	1929	400	-
Total gloves	4118	9120	3482	568	3529	7365	3882
Air filter (µg prothioconazole/ sample)							
1st Mixing/loading	0.1	0.1	0.1	0.1	0.1	0.1	0.1
1st Application	0.1	0.1	0.1	0.1	0.1	0.1	0.1
2nd Mixing/loading	0.1	0.1	0.1	0.1	0.1	0.1	0.1
2nd Application	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Total inhalation dosimeters	0.4	0.4	0.4	0.4	0.4	0.4	0.4

Values in red are <LOQ and have been reported at the LOQ

* During the study a number of handwash samples in esemtam were taken. If multiply samples were < LOQ, these have been summed together assuming each sample was at the LOQ (e.g. if there are 3 samples < LOQ, these have been reported at 3 × LOQ (i.e. 15 µg)

Values corrected for 85% recovery (applicable to the 10000 µg/sample spiking level for gloves)

Table 22: Summary of estimated systemic exposure to prothioconazole

Operator	A	B	C	D	E	F	H
Bodyweight (kg)	82	110	118	84	95	93	120
Outer clothing (mg)	0.21000	0.34400	4.88000	0.21500	0.85100	0.34800	3.40400
Inner clothing (mg)	0.03900	0.03000	0.03200	0.03000	0.03000	0.03000	0.03600
Head (mg)	0.05000	0.00000	0.05000	0.05000	0.00000	0.00000	0.00000
Hands (mg)	0.01680	0.03000	0.01230	0.01000	0.01220	0.01500	0.01000
Nitrile gloves (mg)	4.11765	9.12941	3.48235	0.56824	3.52941	7.36471	3.88235
Air sampler (mg)	0.00040	0.00040	0.00040	0.00040	0.00040	0.00040	0.00040
PDE_{body} (mg/person)	0.29900	0.37400	4.96200	0.29500	0.88100	0.37800	3.44000
PDE_{hands} (mg/person)	4.13445	9.15941	3.49465	0.57824	3.54161	7.37971	3.89235
ADE_{body} (mg/person)	0.08900	0.03000	0.08200	0.08000	0.03000	0.03000	0.03600
ADE_{hands} (mg/person)	0.01680	0.03000	0.01230	0.01000	0.01220	0.01500	0.01000
PIE (mg/person)	0.00416	0.00416	0.00416	0.00416	0.00416	0.00416	0.00416
PDE (mg/person)	4.43345	9.53341	8.45665	0.87324	4.42261	7.75771	7.33235
ADE (mg/person)	0.10580	0.06000	0.09430	0.09000	0.04220	0.04500	0.04600
PIE (mg/kg)	0.00005	0.00004	0.00004	0.00005	0.00004	0.00004	0.00003
PDE (mg/kg)	0.05407	0.08667	0.07167	0.01040	0.04655	0.08342	0.06110
ADE (mg/kg)	0.00129	0.00055	0.00080	0.00107	0.00044	0.00048	0.00038

PIE= Potential inhalation exposure,
PDE=Potential Dermal Exposure (naked),
ADE=Actual dermal exposure (one layer of clothing + gloves during mixing and loading and when handling contaminated surfaces)

Table 23: Summary of prothioconazole-desthio residues found in each sampling dosimeter (corrected for field recoveries)

Operator number	A	B	C	D	E	F	H
Body weight (kg)	82	110	118	84	95	93	120
Area treated (ha)	23	64	180	60	30.3	35	80
Exposure time (mins)	427	317	515	287	520	457	350
Prothioconazole handled (kg)	4.6	12.8	31.3	12	5.6	7.1	15
Prothioconazole applied (kg)	4.6	12.8	31.3	12	5.6	6.9	15
Outer clothing (µg prothioconazole-desthio/ sample)							
Sleeves	51	20	206	20	217	21	54
Shirt torso	78	20	64	20	34	20	23
Trousers torso	20	20	70	20	20	20	20
Legs	28	32	189	26	35	27	20
Total outer clothing	177	92	529	86	306	88	117
Inner clothing (µg prothioconazole-desthio/ sample)							
Sleeves	2	2	5.3	2	3.9	2	2
Torso	2	2	3.7	2	2	2	2
Legs	2	2	2.6	2	2	2	2
Total inner clothing	6	6	11.6	6	7.9	6	6
Cap (µg prothioconazole-desthio/ sample)							
Total head	20	-	20	20	-	-	-
Hand wash (µg prothioconazole-desthio/ sample)							
Hand washings in esemtan*	4	17.3	10.3	2	5.5	4	5.1
Hand washings in isopropanol	2	2	10	2	2.5	2	2
Total hand washing	6	19.3	20.3	4	8	6	7.1
Nitrile gloves rinsings (µg prothioconazole-desthio/ sample)							
Nitrile gloves rinsings (m/L)	383	199	99	80	95	334	215
Nitrile gloves rinsings (application)	105	-	-	-	344	28	-
Total gloves	487	199	99	80	439	362	215
Air filter (µg prothioconazole-desthio/ sample)							
1st Mixing/loading	0.1	0.1	0.1	0.1	0.1	0.1	0.1
1st Application	0.1	0.1	0.1	0.1	0.1	0.1	0.1
2nd Mixing/loading	0.1	0.1	0.1	0.1	0.1	0.1	0.1
2nd Application	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Total inhalation dosimeters	0.4	0.4	0.4	0.4	0.4	0.4	0.4

Values in red are <LOQ and have been reported at the LOQ

** During the study a number of hand wash samples in esemtam were taken. If multiple samples were < LOQ these have been summed together assuming each sample was at the LOQ (e.g. if there are 3 samples < LOQ, these have been reported at 3 x LOQ (i.e. 15 µg)

Shading	Meaning
(blue)	values corrected for 92% recovery (applicable to the 10 ug/sample spiking level for inner clothing
(tan)	values corrected for 89% recovery (applicable to the 0.04 µg/mL spiking level for hand wash)
(green)	values corrected for 87% recovery (applicable to the 3000 µg/sample spiking level for gloves)

Table 24: Summary of estimated systemic exposure to prothioconazole-desthio

Operator	A	B	C	D	E	F	H
Bodyweight (kg)	82	110	118	84	95	93	120
Outer clothing (mg)	0.1770	0.0920	0.5290	0.0860	0.3060	0.0880	0.1170
Inner clothing (mg)	0.0060	0.0060	0.0116	0.0060	0.0079	0.0060	0.0060
Head (mg)	0.0200	0.0000	0.0200	0.0200	0.0000	0.0000	0.0000
Hands (mg)	0.0060	0.0193	0.0203	0.0040	0.0080	0.0060	0.0071
Nitrile gloves (mg)	0.3828	0.1989	0.0989	0.0805	0.0954	0.3345	0.2149
Air sampler (mg)	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004
PDE_{body} (mg/person)	0.2030	0.0980	0.5606	0.1120	0.3139	0.0940	0.1230
PDE_{hands} (mg/person)	0.3888	0.2182	0.1192	0.0845	0.1034	0.3405	0.2220
ADE_{body} (mg/person)	0.0260	0.0060	0.0316	0.0260	0.0079	0.0060	0.0060
ADE_{hands} (mg/person)	0.0060	0.0193	0.0203	0.0040	0.0080	0.0060	0.0071
PIE (mg/person)	0.00416	0.00416	0.00416	0.00416	0.00416	0.00416	0.00416
PDE (mg/person)	0.59180	0.31620	0.67980	0.19650	0.41730	0.43450	0.34500
ADE (mg/person)	0.03200	0.02530	0.05190	0.03000	0.01590	0.01200	0.01310
PIE (mg/kg)	0.00005	0.00004	0.00004	0.00005	0.00004	0.00004	0.00003
PDE (mg/kg)	0.00722	0.00287	0.00576	0.00234	0.00439	0.00467	0.00288
ADE (mg/kg)	0.00039	0.00023	0.00044	0.00036	0.00017	0.00013	0.00011

PIE= Potential inhalation exposure,
PDE=Potential Dermal Exposure (naked),
ADE=Actual dermal exposure (one layer of clothing + gloves during mixing and loading and when handling contaminated surfaces)

III Conclusion

A final conclusion of all spray application results are given under "overall summary and conclusions".

Overall summary and conclusions

All studies were designed as mixer/loader/applicator-studies as this type of study reflects best the real work situation of farmers in Europe when performing ground boom spraying. In total, twenty replicates – performed by fifteen operators – were monitored.

The first study – conducted in 2000 – had to be performed under confined conditions as the active substance was still under development. Therefore, the area treated was restricted to 20 ha, nevertheless different types of application equipment were used. Three Bayer employees were involved as operators.

The second study was conducted in 2005. As prothioconazole had received national approval at that time the study was conducted with five professional farmers in their fields.

In the third study seven professional farmers represented the operators spraying prothioconazole containing products in their fields.

In the tables below study parameters are shown in a detailed as well as in a summary form. From the overview it can be concluded that the study conditions really cover all parameters encountered in Europe with regard to downward directed boom spraying:

- areas ranging from 19 ha to 80 ha, one replicate even at 180 ha;
- boom widths ranging from 15 m (to be unfolded/folded manually and automatically) up to 36 m with a self-propelled sprayer;
- spray tank volumes ranging from 800 L up to 4000 L.

The tractors were equipped with a cabin as it is standard practice nowadays.

Table 25: Study parameters of replicates

Study	Operator ID	Area treated [ha]	Equipment	No. of tasks load // appl.
01	A1	20	Tractor-drawn boom 28 m, 2500 L spray tank	2 // 2
01	B1	20	Tractor-drawn boom 28 m, 2500 L spray tank	2 // 2
01	C1	20	Tractor-drawn boom 28 m, 2500 L spray tank	2 // 2
01	B2	20	Tractor-drawn boom 28 m, 2500 L spray tank	2 // 2
01	C2	20	Tractor-drawn boom 28 m, 2500 L spray tank	2 // 2
01	A3	20	Tractor-mounted boom 15 m, 800 L spray tank	6 // 6
01	C3	20	Tractor-mounted boom 15 m, 800 L spray tank	6 // 6
01	B3	20	Tractor-mounted boom 15 m, 800 L spray tank	6 // 6
02	A	67	Tractor-drawn boom 30 m, 4000 L spray tank	4 // 4
02	B	19	Tractor-mounted boom 15 m (manual folding), 1000 L tank	4 // 4
02	C	33	Tractor-mounted boom 15 m, 1100 L spray tank	7 // 6
02	D	49	Tractor-drawn boom 18 m, 3000 L spray tank	3 // 3
02	E	25	Tractor-mounted boom 15 m, 1000 L spray tank	6 // 6
03	A	23	Tractor-mounted boom 15 m (manual folding), 840 L tank	9 // 9
03	B	64	Self-propelled 24 m boom, 4000 L spray tank	4 // 4
03	C	180	Self-propelled 36 m boom, 4000 L spray tank	14 // 14
03	D	60	Self-propelled 24 m boom, 2600 L spray tank	6 // 6
03	E	30	Tractor-mounted boom 15 m (manual folding), 1000 L tank	6 // 6
03	F	35	Tractor-mounted boom 21 m, 1500 L spray tank	8 // 8
03	H	80	Tractor-drawn boom 24 m, 4000 L spray tank	**2** // 4

Table 26: Summary of study parameters

Parameter	Study parameter
Formulation	250 g/L prothioconazole (Proline EC)/ 160 g/L prothioconazole (Input EC)
Crop	Cereals/canola (1 application)
No. of replicates	15 operators/20 replicates (at 13 locations) combined work cycles (mix/load/application)
Application technique	Downward directed boom sprayer: Tractor (closed cabin) + boom (15 – 36 m boom)
Time	1.9 – 8.7 h (mean: 5 h, all data) 4.8 – 8.7 h (mean: 6.7 h with reports MR-156/05 and MR-244/07)
Area treated	19 – 180 ha/day (mean: 41 ha, all data; 55 ha with reports MR-156/05 and MR-244/07)
Application rate	175 g (canola) – 200 g prothioconazole/ha
Water volume	150 to 300 L/ha
Total a.s. handled	4 to 31.3 kg a.s./day
In-use concentration	0.8 to 1.5 g a.s./L
PPE/clothing	Nitrile gloves: during mixing/loading, during application only if necessary (e.g., when handling contaminated surfaces); one layer of clothing

Although detailed exposure data from the studies are not presented in this overview some general observations are summarised nevertheless.

It is remarkable that though 17 replicates (out of 20) had measurable residues of prothioconazole on their outer clothing only three operators showed measurable residues of prothioconazole on their undergarments.
For prothioconazole-desthio in 15 out of 20 replicates measurable residues were found on the outer clothing but only three operators showed measurable residues on their undergarments.
Only one of the operators had measured residues of both prothioconazole and prothioconazole-desthio concurrently on his undergarments.
Exposure of the head was determined for 15 replicates (out of 20). In all cases – for prothioconazole as well as for prothioconazole-desthio – the results were "<LOQ".
Hence, it is acceptable that these results can also be extrapolated to the other five replicates to calculate a hypothetical head exposure.
The results of the protective gloves show higher exposure figures for the first study as compared to the second and the third. The reason for this is mainly due to the fact that most of the farmers in study 02 and study 03 (who had the possibility) rinsed the gloves under water before taking them off. This is in accordance with good occupational hygiene practice and therefore, any farmer who was going to behave like this was let to proceed as he was used to.
However, one should be aware that residues on protective gloves should be regarded to have an indicative character only, similar to the residues on outer clothing or estimates of potential dermal exposure. Essential figures for risk assessments should always relate to real, actual dermal exposure data whenever they are available.
The potential and actual dermal exposure figures as well as the inhalation results from all studies are listed in the tables below for the exposure to prothioconazole and for the exposure to prothioconazole-desthio. Normalization was performed with regard to the actual bodyweight of the individual operators as well as to kg active substance handled.

Table 27: Exposure to prothioconazole

Operator ID	Body weight	Prothioconazole [mg/person/day]			Prothioconazole [mg/kg bw]		
		PDE	ADE	IE	PDE	ADE	IE
A1	95	2.8969000	0.0850000	0.0083200	0.0304937	0.0008947	0.0000876
B1	80	7.1461000	0.0850000	0.0084700	0.0893263	0.0010625	0.0001059
C1	72	5.2388000	0.0850000	0.0083200	0.0727611	0.0011806	0.0001156
B2	80	2.5628000	0.0850000	0.0083200	0.0320350	0.0010625	0.0001040
C2	72	20.9089000	0.0874000	0.0083200	0.2904014	0.0012139	0.0001156
A3	95	15.8807000	0.0900000	0.0041600	0.1671653	0.0009474	0.0000438
C3	72	30.0888000	0.0908000	0.0041600	0.4179000	0.0012611	0.0000578
B3	80	19.5956000	0.0900000	0.0041600	0.2449450	0.0011250	0.0000520
A	75	15.5482000	0.2789000	0.0049600	0.2073093	0.0037187	0.0000661
B	100	5.5794000	0.0950000	0.0020800	0.0557940	0.0009500	0.0000208
C	85	12.0797000	0.1000000	0.0041600	0.1421141	0.0011765	0.0000489
D	85	1.9019000	0.1000000	0.0020800	0.0223753	0.0011765	0.0000245
E	80	2.4181000	0.0450000	0.0020800	0.0302263	0.0005625	0.0000260
A	82	4.4334500	0.1058000	0.0041600	0.0540665	0.0012902	0.0000507
B	110	9.5334100	0.0600000	0.0041600	0.0866674	0.0005455	0.0000378
C	118	8.4566500	0.0943000	0.0041600	0.0716665	0.0007992	0.0000353
D	84	0.8732400	0.0900000	0.0041600	0.0103957	0.0010714	0.0000495
E	95	4.4226100	0.0422000	0.0041600	0.0465538	0.0004442	0.0000438
F	93	7.7577100	0.0450000	0.0041600	0.0834162	0.0004839	0.0000447
H	120	7.3323500	0.0460000	0.0041600	0.0611029	0.0003833	0.0000347
Mean		9.2327660	0.0900200	0.0049355	0.1108358	0.0010675	0.0000582
75th percentile		12.9468250	0.0944750	0.0058000	0.1483769	0.0011775	0.0000715
75th parametric estimate		13.7290000	0.1101000	0.0062000	0.1441000	0.0013000	0.0000740
95th percentile		21.3678950	0.1144550	0.0083275	0.2967763	0.0014117	0.0001156
95th parametric estimate		32.4870000	0.1720000	0.0099000	0.3898000	0.0023000	0.0001270

PDE: Potential dermal exposure (= Sum of outer clothing, inner clothing, hand and glove washing, head)
ADE: Actual dermal exposure (= Sum of inner clothing, hand washing, head)
IE: Inhalation exposure (Breathing rate 20.8 L/min)

Table 28: Exposure to prothioconazole-desthio

Operator ID	Body weight	Prothioconazole-desthio [mg/person/day] PDE	ADE	IE	Prothioconazole-desthio [mg/kg bw] PDE	ADE	IE
A1	95	0.1663000	0.0280000	0.0083200	0.0017505	0.0002947	0.0000876
B1	80	0.2110000	0.0280000	0.0083200	0.0026375	0.0003500	0.0001040
C1	72	0.1959000	0.0280000	0.0083200	0.0027208	0.0003889	0.0001156
B2	80	0.3625000	0.0280000	0.0083200	0.0045313	0.0003500	0.0001040
C2	72	0.7141000	0.0280000	0.0083200	0.0099181	0.0003889	0.0001156
A3	95	2.6452000	0.0300000	0.0041600	0.0278442	0.0003158	0.0000438
C3	72	4.2943000	0.0300000	0.0041600	0.0596431	0.0004167	0.0000578
B3	80	3.5272000	0.0361000	0.0041600	0.0440900	0.0004513	0.0000520
A	75	1.3632000	0.1599000	0.0020800	0.0181760	0.0021320	0.0000277
B	100	0.4207000	0.0327000	0.0020800	0.0042070	0.0003270	0.0000208
C	85	0.8435000	0.0340000	0.0041600	0.0099235	0.0004000	0.0000489
D	85	0.1881000	0.0340000	0.0020800	0.0022129	0.0004000	0.0000245
E	80	0.2073000	0.0320000	0.0020800	0.0025913	0.0004000	0.0000260
A	82	0.5918000	0.0320000	0.0041600	0.0072171	0.0003902	0.0000507
B	110	0.3162000	0.0253000	0.0041600	0.0028745	0.0002300	0.0000378
C	118	0.6798000	0.0519000	0.0041600	0.0057610	0.0004398	0.0000353
D	84	0.1965000	0.0300000	0.0041600	0.0023393	0.0003571	0.0000495
E	95	0.4173000	0.0159000	0.0041600	0.0043926	0.0001674	0.0000438
F	93	0.4345000	0.0120000	0.0041600	0.0046720	0.0001290	0.0000447
H	120	0.3450000	0.0131000	0.0041600	0.0028750	0.0001092	0.0000347
Mean		0.9060200	0.0354450	0.0047840	0.0110189	0.0004219	0.0000562
75th percentile		0.7464500	0.0330250	0.0052000	0.0099194	0.0004000	0.0000652
75th parametric estimate		1.0461580	0.0432670	0.0060220	0.0122850	0.0005180	0.0000710
95th percentile		3.5655550	0.0573000	0.0083200	0.0448677	0.0005353	0.0001156
95th parametric estimate		3.0146100	0.0754720	0.0100050	0.0369500	0.0009730	0.0001250

PDE: Potential dermal exposure (= Sum of outer clothing, inner clothing, hand and glove washing, head)
ADE: Actual dermal exposure (=Sum of inner clothing, hand washing, head)
IE: Inhalation exposure (Breathing rate 20.8 L/min)

CP 7.2.2 Bystander and resident exposure

CP 7.2.2.1 Estimation of bystander and resident exposure

A summary of the exposure models used for the estimation of resident exposure to the active substances during application of BIX + FLU + PTZ EC 260 according to the representative use is presented in the following.

Table 29: Exposure models for intended uses

Critical use(s)	1.2 L / kg product/ha for Cereals
Model	*Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874*

Regarding the resident exposure to direct drift, exposure calculations are performed for ground boom sprayer for low crops.
With respect to resident exposure via direct drift the default drift values proposed by the EFSA guidance refer to the BREAModel (Bystander and Resident Exposure Assessment Model). It should be noted that the model has recently been updated with independent support by the HSE's Chemical Regulation Division (CRD). The drift values to estimate subchronic potential dermal exposure as suggested by BREAM2 for ground boom spray applications when using standard nozzle types are presented in the following table.

Table 30: Default potential exposure from spray drift [mL/person] proposed by BREAM2 concerning subchronic exposure

Person	BREAM2 proposed default values	
	Potential dermal exposure from spray drift [mL/person]	
	75th percentile	mean
Adult:	0.252	0.185
Child:	0.183	0.133
	Potential inhalation exposure from spray drift [mL/person]	
Adult:	0.000443	0.000383
Child:	0.000926	0.000721

Hence, with a reasonable approach exposure estimates considering the revised default drift values from BREAM2 are presented as well. For more details about BREAM2 please refer to:
https://www.ssau.co.uk/bream2-calculator.
For the active substances Fluopyram, Bixafen and Prothioconazole measured crop specific DFR data are available. Measured DFR data are as well available for prothioconazole-desthio. The DFR data are taken into account to refine the resident "entry into treated crop" scenario. For details please refer to Detailed evaluation of DFR study relied upon.
Furthermore, here again it has to be mentioned that after foliar spray application of Prothioconazole-containing products diluted Prothioconazole can degrade to prothioconazole-desthio on plant surfaces, clothing or skin. Accordingly, although prothioconazole-desthio is not part of the formulation per se non-dietary risk assessments are always performed for prothioconazole-desthio due to its toxicological properties.

For the first tier evaluation a conservative approach was applied and the following assumptions were used in the exposure calculations for the exposure risk of residents to prothioconazole-desthio:

- For the exposure assessment to prothioconazole-desthio a 100% conversion of Prothioconazole to prothioconazole-desthio is assumed. When calculating the amount of prothioconazole-desthio a conversion factor of 0.907 is applied (based on a molecular weight of 344.254 g/mol for Prothioconazole and 312.194 g/mol for prothioconazole-desthio).
- No conversion of Prothioconazole to prothioconazole-desthio was considered for the exposure assessment to Prothioconazole.

However, to achieve a more accurate risk evaluation the exposure assessments should always consider measured data whenever such data are available. Thus, resident exposure to Prothioconazole and prothioconazole-desthio is further assessed based on measured data. For further details concerning the

refined exposure assessments for prothioconazole-desthio please refer CP 7.2.2.2 Measurement of bystander and resident exposure.

The tier 1 assessment according to the EFSA default approach the outcome of the estimations is presented in the following tables. Furthermore, refined exposure estimates regarding the "Entry into treated crop" scenario are shown which consider measured DFR values. Detailed calculations are presented in Table 31 to Table 38.

Table 31: Estimated resident exposure, Fluopyram, Cereals

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.078 kg a.s./ha, 365 days interval, Minimum water volume: 200 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.00175	3.51	0.000833	0.00733	14.7	0.00404
Vapour	0.00023	0.46	0.00023	0.00107	2.14	0.00107
Surface deposits	0.000372	0.744	0.000272	0.000858	1.72	0.000628
Entry into treated crops[4]	0.0512	10.2	0.00408	0.00921	18.4	0.00735
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00542 (10.8%)			0.0131 (26.2%)
Entry into treated crops[5]	0.00152	3.06	0.00122	0.00275	5.5	0.00219
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00255 (5.11%)			0.00793 (15.9%)

[1] AOEL (RVNAS) of FLU: 0.05 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 2-3 m distance
[4] Default DFR = 3
[5] Measured DFR = 0.896

Table 32: Estimated resident exposure, Bixafen, Cereals

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.078 kg a.s./ha, 365 days interval, Minimum water volume: 200 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.00175	1.35	0.000833	0.00733	5.64	0.00404
Vapour	0.00023	0.177	0.00023	0.00107	0.823	0.00107
Surface deposits	0.000372	0.286	0.000272	0.000858	0.66	0.000628
Entry into treated crops[4]	0.00512	3.94	0.00408	0.00921	7.09	0.00735
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00542 (4.17%)			0.0131 (10.1%)
Entry into treated crops[5]	0.00176	1.35	0.0014	0.00317	2.44	0.00252
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00274 (2.11%)			0.00826 (6.35%)

[1] AOEL (RVNAS) of BIX: 0.13 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 2-3 m distance
[4] Default DFR = 3
[5] Measured DFR = 1.031

Table 33: Estimated resident exposure, Prothioconazole, Cereals

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.156 kg a.s./ha, 365 days interval, Minimum water volume: 200 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.00351	1.75	0.00167	0.0147	7.33	0.00807
Vapour	0.00023	0.115	0.00023	0.00107	0.535	0.00107
Surface deposits	0.000744	0.372	0.000545	0.00172	0.858	0.00126
Entry into treated crops[4]	0.0102	5.12	0.00816	0.0184	9.21	0.0147
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.0106 (5.3%)			0.0251 (12.5%)
Entry into treated crops[5]	0.00174	0.87	0.00139	0.00312	1.57	0.0025
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00383 (1.91%)			0.0129 (6.45%)

[1] AOEL (RVNAS) of PTZ: 0.2 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 2-3 m distance
[4] Default DFR = 3
[5] Measured DFR = 0.51

Table 34: Estimated resident exposure, PTZ-Desthio, Cereals

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.141 kg a.s./ha, 365 days interval, Minimum water volume: 200 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.002	20	0.00095	0.00836	83.6	0.00461
Vapour	0.00023	2.3	0.00023	0.00107	10.7	0.00107
Surface deposits	0.000424	4.24	0.000311	0.00102	10.2	0.00074
Entry into treated crops[4]	0.00584	58.4	0.00465	0.0105	105	0.00838
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00614 (61.4%)			0.0448 (148%)
Entry into treated crops[5]	0.00134	13.4	0.00107	0.00241	24.1	0.00192
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00236 (25.6%)			0.00835 (83.5%)

[1] AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 2-3 m distance
[4] Default DFR = 3
[5] Measured DFR = 0.689

Results considering the revised default drift values from BREAM2 are presented in the following.

Table 35: Estimated resident exposure, Fluopyram, Cereals, considering revised default spray drift values from BREAM2

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.078 kg a.s./ha, 365 days interval, Minimum water volume 200 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.000943	1.89	0.000693	0.00413	8.27	0.00301
Vapour	0.00023	0.46	0.00023	0.00107	2.14	0.00107
Surface deposits	0.000372	0.744	0.000272	0.000858	1.72	0.00062 8
Entry into treated crops[4]	0.00512	10.2	0.00408	0.00921	18.4	0.00735
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00528 (10.6%)			0.0121 (24.1%)
Entry into treated crops[5]	0.00153	3.06	0.00122	0.00275	5.5	0.00219
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00241 (4.83%)			0.0069 (13.8%)

[1] AOEL (RVNAS) of FLU: 0.05 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 2-3 m distance
[4] Default DFR = 3
[5] Measured DFR = 0.896

Table 36: Estimated resident exposure, Bixafen, Cereals, considering revised default spray drift values from BREAM2

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.078 kg a.s./ha, 365 days interval, Minimum water volume: 200 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.000943	0.725	0.000693	0.00413	3.18	0.00301
Vapour	0.00023	0.177	0.00023	0.00107	0.823	0.00107
Surface deposits	0.000372	0.286	0.000272	0.000858	0.66	0.00062 8
Entry into treated crops[4]	0.00512	3.94	0.00408	0.00921	7.09	0.00735
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00528 (4.06%)			0.0121 (9.27%)
Entry into treated crops[5]	0.00176	1.35	0.0014	0.00317	2.44	0.00252
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.0026 (2%)			0.00723 (5.56%)

[1] AOEL (RVNAS) of BIX: 0.13 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 2-3 m distance
[4] Default DFR = 3
[5] Measured DFR = 1.031

Table 37: Estimated resident exposure, Prothioconazole, Cereals, considering revised default spray drift values from BREAM2

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.156 kg a.s./ha, 365 days interval, Minimum water volume: 200 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.00189	0.943	0.00139	0.00827	4.13	0.00601
Vapour	0.00023	0.115	0.00023	0.00107	0.535	0.00107
Surface deposits	0.000744	0.372	0.000545	0.00172	0.858	0.00126
Entry into treated crops[4]	0.0102	5.12	0.00816	0.0184	9.21	0.0147
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.0103 (5.16%)			0.023 (11.5%)
Entry into treated crops[5]	0.00174	0.87	0.00139	0.00313	1.57	0.0025
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00355 (1.77%)			0.0108 (5.42%)

[1] AOEL (RVNAS) of PTZ: 0.2 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 2-3 m distance
[4] Default DFR = 3
[5] Measured DFR = 0.5

Table 38: Estimated resident exposure, prothioconazole-desthio, Cereals, considering revised default spray drift values from BREAM2

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.141 kg a.s./ha, 365 days interval, Minimum water volume: 200 L/ha						
Routes of exposure	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)	**75th centile** (mg/kg bw/day)	**in % of AOEL[1] (RVNAS)**	**Mean** (mg/kg bw/day)
Spray drift[3]	0.00108	10.8	0.000791	0.00474	47.4	0.00345
Vapour	0.00023	2.3	0.00023	0.00107	10.7	0.00107
Surface deposits	0.000424	4.24	0.000311	0.00102	10.2	0.00074
Entry into treated crops[4]	0.00584	58.4	0.00465	0.00105	105	0.00838
Sum of all pathways: default DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00599 (59.9%)			0.0136 (136%)
Entry into treated crops[5]	0.00124	13.4	0.00107	0.00241	24.1	0.00192
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.0024 (24%)			0.00719 (71.9%)

[1] AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 2-3 m distance
[4] Default DFR = 3
[5] Measured DFR = 0.689

Bystander and Resident exposure calculations (KCP 7.2.3.1)

Table 39: Bystander and resident exposure, Fluopyram, Cereals

Substance	Fluopyram	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.078 kg a.s. /ha	**Spray dilution =** 0.39 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.05 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day		% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day		% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00733	% of RVNAS[1]	14.7%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	2.14%
	Surface deposits (75th percentile) mg/kg bw/day	0.000858	% of RVNAS[1]	1.72%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00921	% of RVNAS[1]	18.4%
	All pathways (mean) mg/kg bw/day	0.0131	% of RVNAS[1]	26.2%
Resident adult	Spray drift (75th percentile) mg/kg bw/day	0.00175	% of RVNAS[1]	3.51%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	0.46%
	Surface deposits (75th percentile) mg/kg bw/day	0.000372	% of RVNAS[1]	0.744%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00512	% of RVNAS[1]	10.2%
	All pathways (mean) mg/kg bw/day	0.00542	% of RVNAS[1]	10.8%

Measured DFR	0.896 µg a.s./cm² per kg a.s./ha			
Resident – child (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00275	% of RVNAS[1]	5.5%
	All pathways (mean) mg/kg bw/day	0.00793	% of RVNAS[1]	15.9%
Resident – adult (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00153	% of RVNAS[1]	2.06%
	All pathways (mean) mg/kg bw/day	0.00255	% of RVNAS[1]	5.11%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 40: Bystander and resident exposure, Prothioconazole, Cereals

Substance	Prothioconazole	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.156 kg a.s. /ha	**Spray dilution =** 0.78 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.2 mg/kg bw/day		RVAAS[2]	mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.0147	% of RVNAS[1]	7.33%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	0.535%
	Surface deposits (75th percentile) mg/kg bw/day	0.00172	% of RVNAS[1]	0.858%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0184	% of RVNAS[1]	9.21%
	All pathways (mean) mg/kg bw/day	0.0251	% of RVNAS[1]	12.5%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.00351	% of RVNAS[1]	1.75%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	0.115%
	Surface deposits (75th percentile) mg/kg bw/day	0.000744	% of RVNAS[1]	0.372%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0102	% of RVNAS[1]	5.12%
	All pathways (mean) mg/kg bw/day	0.0106	% of RVNAS[1]	5.3%

Measured DFR	0.51 µg a.s./cm² per kg a.s./ha			
Resident – child (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00313	% of RVNAS[1]	1.57%
	All pathways (mean) mg/kg bw/day	0.0129	% of RVNAS	6.45%
Resident – adult (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00174	% of RVNAS[1]	0.87%
	All pathways (mean) mg/kg bw/day	0.00383	% of RVNAS[1]	1.91%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 41: Bystander and resident exposure, Bixafen, Cereals

Substance	Bixafen	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.078 kg a.s. /ha	**Spray dilution =** 0.39 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.13 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00733	% of RVNAS[1]	5.64%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	0.823%
	Surface deposits (75th percentile) mg/kg bw/day	0.000858	% of RVNAS[1]	0.66%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00921	% of RVNAS[1]	7.09%
	All pathways (mean) mg/kg bw/day	0.0131	% of RVNAS[1]	10.1%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.00175	% of RVNAS[1]	1.35%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	0.177%
	Surface deposits (75th percentile) mg/kg bw/day	0.000372	% of RVNAS[1]	0.286%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00512	% of RVNAS[1]	3.94%
	All pathways (mean) mg/kg bw/day	0.00542	% of RVNAS[1]	4.17%

Measured DFR	1.031 µg a.s./cm² per kg a.s./ha			
Resident – child (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00317	% of RVNAS[1]	2.44%
	All pathways (mean) mg/kg bw/day	0.00826	% of RVNAS	6.35%
Resident – adult (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00176	% of RVNAS[1]	1.35%
	All pathways (mean) mg/kg bw/day	0.00274	% of RVNAS[1]	2.11%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 42: Bystander and resident exposure, PTZ-Desthio, Cereals

Substance	PTZ-Desthio	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.141 kg a.s. /ha	**Spray dilution =** 0.705 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = -%	**Dermal for in use dilution** = 44%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.01 mg/kg bw/day		RVAAS	mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00836	% of RVNAS[1]	83.6%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	10.7%
	Surface deposits (75th percentile) mg/kg bw/day	0.00102	% of RVNAS[1]	10.2%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0105	% of RVNAS[1]	105%
	All pathways (mean) mg/kg bw/day	0.0148	% of RVNAS[1]	148%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.002	% of RVNAS[1]	20%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	2.3%
	Surface deposits (75th percentile) mg/kg bw/day	0.000424	% of RVNAS[1]	4.24%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00584	% of RVNAS[1]	58.4%
	All pathways (mean) mg/kg bw/day	0.00614	% of RVNAS[1]	61.4%

Measured DFR	0.689 µg a.s./cm² per kg a.s./ha			
Resident – child (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00241	% of RVNAS[1]	24.1%
	All pathways (mean) mg/kg bw/day	0.00835	% of RVNAS	83.5%
Resident – adult (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00134	% of RVNAS[1]	12.4%
	All pathways (mean) mg/kg bw/day	0.00256	% of RVNAS[1]	25.6%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 43: Bystander and resident exposure, Fluopyram, Cereals, considering revised default spray drift values from BREAM2

Substance	Fluopyram	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.078 kg a.s. /ha	**Spray dilution =** 0.39 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of < 5*10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.05 mg/kg bw/day		RVNAS[2]	- mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00413	% of RVNAS[1]	8.27%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	2.14%
	Surface deposits (75th percentile) mg/kg bw/day	0.000858	% of RVNAS[1]	1.72%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00921	% of RVNAS[1]	18.4%
	All pathways (mean) mg/kg bw/day	0.0121	% of RVNAS[1]	24.1%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.000943	% of RVNAS[1]	1.89%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	0.46%
	Surface deposits (75th percentile) mg/kg bw/day	0.000372	% of RVNAS[1]	0.744%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00512	% of RVNAS[1]	10.2%
	All pathways (mean) mg/kg bw/day	0.00528	% of RVNAS[1]	10.6%

Measured DFR	0.896 µg a.s./cm² per kg a.s./ha			
Resident – child (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00275	% of RVNAS[1]	5.5%
	All pathways (mean) mg/kg bw/day	0.0069	% of RVNAS[1]	13.8%
Resident – adult (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00153	% of RVNAS[1]	2.06%
	All pathways (mean) mg/kg bw/day	0.00241	% of RVNAS[1]	4.83%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 44: Bystander and resident exposure, Bixafen, Cereals, considering revised default spray drift values from BREAM2

Substance	Bixafen	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.078 kg a.s. /ha	**Spray dilution =** 0.39 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of < 5*10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.13 mg/kg bw/day		RVNAS[2]	- mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00413	% of RVNAS[1]	3.18%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	0.823%
	Surface deposits (75th percentile) mg/kg bw/day	0.000858	% of RVNAS[1]	0.66%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00921	% of RVNAS[1]	7.09%
	All pathways (mean) mg/kg bw/day	0.0121	% of RVNAS[1]	9.27%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.000943	% of RVNAS[1]	0.725%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	0.177%
	Surface deposits (75th percentile) mg/kg bw/day	0.000372	% of RVNAS[1]	0.286%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00512	% of RVNAS[1]	3.94%
	All pathways (mean) mg/kg bw/day	0.00528	% of RVNAS[1]	4.06%

Measured DFR	1.031 µg a.s./cm² per kg a.s./ha			
Resident – child (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00317	% of RVNAS[1]	2.44%
	All pathways (mean) mg/kg bw/day	0.00723	% of RVNAS	5.56%
Resident – adult (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00176	% of RVNAS[1]	1.35%
	All pathways (mean) mg/kg bw/day	0.0026	% of RVNAS[1]	2%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 45: Bystander and resident exposure, Prothioconazole, Cereals, considering revised default spray drift values from BREAM2

Substance	Prothioconazole	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.156 kg a.s. /ha	**Spray dilution =** 0.78 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of > 10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.2 mg/kg bw/day		RVNAS[2]	- mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00825	% of RVNAS[1]	4.13%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	0.535%
	Surface deposits (75th percentile) mg/kg bw/day	0.00172	% of RVNAS[1]	0.858%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0184	% of RVNAS[1]	9.21%
	All pathways (mean) mg/kg bw/day	0.023	% of RVNAS[1]	11.5%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.00189	% of RVNAS[1]	0.943%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	0.115%
	Surface deposits (75th percentile) mg/kg bw/day	0.000744	% of RVNAS[1]	0.372%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0102	% of RVNAS[1]	5.12%
	All pathways (mean) mg/kg bw/day	0.0103	% of RVNAS[1]	5.16%

Measured DFR	0.51 µg a.s./cm² per kg a.s./ha			
Resident – child (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00313	% of RVNAS[1]	1.57%
	All pathways (mean) mg/kg bw/day	0.0108	% of RVNAS	5.42%
Resident – adult (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00174	% of RVNAS[1]	0.87%
	All pathways (mean) mg/kg bw/day	0.00355	% of RVNAS[1]	1.77%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 46: Bystander and resident exposure, prothioconazole-desthio, Cereals, considering revised default spray drift values from BREAM2

Substance	PTZ-Desthio	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.141 kg a.s. /ha	**Spray dilution =** 0.705 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of > 10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = -%	**Dermal for in use dilution** = 44%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.01 mg/kg bw/day		RVNAS[2]	- mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00474	% of RVNAS[1]	47.4%
	Vapour (75th percentile) mg/kg bw/day	0.00107	% of RVNAS[1]	10.7%
	Surface deposits (75th percentile) mg/kg bw/day	0.00102	% of RVNAS[1]	10.2%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0105	% of RVNAS[1]	105%
	All pathways (mean) mg/kg bw/day	0.0136	% of RVNAS[1]	136%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.00108	% of RVNAS[1]	10.8%
	Vapour (75th percentile) mg/kg bw/day	0.00023	% of RVNAS[1]	2.3%
	Surface deposits (75th percentile) mg/kg bw/day	0.000424	% of RVNAS[1]	4.24%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00584	% of RVNAS[1]	58.4%
	All pathways (mean) mg/kg bw/day	0.00599	% of RVNAS[1]	59.9%

Measured DFR	0.689 µg a.s./cm² per kg a.s./ha			
Resident – child (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00241	% of RVNAS[1]	24.1%
	All pathways (mean) mg/kg bw/day	0.00719	% of RVNAS[1]	71.9%
Resident – adult (Measured)	Surface deposits (75th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00134	% of RVNAS[1]	12.4%
	All pathways (mean) mg/kg bw/day	0.0024	% of RVNAS[1]	24%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Conclusion

The bystander/resident exposure estimations carried out indicated that the acceptable Bystander/Resident exposure level (AOEL) will not be exceeded under conditions of intended uses and considering above mentioned personal protective equipment (PPE).
Based on the presented calculation it is demonstrated that no unacceptable risk is given with the intended use of BIX+FLU+PTZ EC 260.

CP 7.2.2.2 Measurement of bystander and resident exposure

It is noted that the exposure estimates considering the EFSA default approach together with measured DFR values regarding "entry into treated crops" are already below the AOEL. The same holds true when considering with respect to spray drift exposure the revised default drift value proposed by BREAM2. Hence from that perspective a further refinement is not necessary.
However, it is noted that in terms of combined exposure the Hazard Index (HI) according to the tier one approach slightly exceeds one when considering the EFSA default approach with re-entry into treated crops refined using measured DFR data (HI all pathways: 1.07). The HI all pathways according to the tier one approach is already within acceptable limits when considering the revised default drift values from BREAM2 (HI all pathways: 0.9251) indicating that even a potentially combined toxicity is of no concern. However, the further refinement is conducted regarding the conversion product prothioconazole- desthio. For the refinements substance as well as crop and use specific (fungicide application in cereals) measured spray drift exposure as well as measured vapour concentrations are considered. The results of the refined evaluations are presented in the following tables. For details please refer to Direct drift: Exposure studies, Spray drift revised and Vapour: Exposure study for Prothioconazole-desthio.

Table 47: **Predicted systemic exposure to prothioconazole-desthio, refined, considers measured actual dermal exposure from spray drift adjusted to EFSA default drift values and measured DFR data regarding entry into treated crops as well as measured vapour concentrations**

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.141 kg a.s./ha, 365 days interval, Minimum water volume: 200 L/ha						
Routes of exposure	**75th centile (mg/kg bw/day)**	**in % of AOEL[1] (RVNAS)**	**Mean (mg/kg bw/day)**	**75th centile (mg/kg bw/day)**	**in % of AOEL[1] (RVNAS)**	**Mean (mg/kg bw/day)**
Spray drift[3] (refined)[4]	0.002	20.0	0.0095	0.00836	83.6	0.00461
Vapour (measured)	0.0000108	0.108	0.0000108	0.0000502	0.502	0.0000502
Surface deposits (acc. to EFSA)	0.000424	4.24	0.000311	0.00102	10.2	0.000748
Entry into treated crops (measured DFR)[5]	0.00172	17.2	0.00137	0.00309	30.9	0.00247
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00264 (26.4%)			0.00788 (78.8%)

[1] AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 2-3 m distance
[4] Considers measured actual dermal exposure from spray drift adjusted to EFSA default drift values
[5] Measured DFR = 0.689

Table 48: Bystander and resident exposure, prothioconazole-desthio, Cereals, considering revised default spray drift values from BREAM2

Substance	PTZ-Desthio	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.141 kg a.s. /ha	**Spray dilution =** 0.705 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of > 10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = -%	**Dermal for in use dilution** = 44%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.01 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	
DFR	0.689 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day		% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day		% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.00836	% of RVNAS[1]	83.6%
	Vapour (75th percentile) mg/kg bw/day	0.0000502	% of RVNAS[1]	0.5%
	Surface deposits (75th percentile) mg/kg bw/day	0.00102	% of RVNAS[1]	10.2%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0309	% of RVNAS[1]	30.9%
	All pathways (mean) mg/kg bw/day	0.00788	% of RVNAS[1]	78.8%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.002	% of RVNAS[1]	20%
	Vapour (75th percentile) mg/kg bw/day	0.0000108	% of RVNAS[1]	0.108%
	Surface deposits (75th percentile) mg/kg bw/day	0.000424	% of RVNAS[1]	4.24%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00172	% of RVNAS[1]	17.2%
	All pathways (mean) mg/kg bw/day	0.00264	% of RVNAS[1]	26.4%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 49: Predicted systemic exposure to prothioconazole-desthio, refined, considers measured actual dermal exposure from spray drift adjusted to BREAM2 default drift values and measured DFR data regarding entry into treated crops as well as measured vapour concentrations

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.141 kg a.s./ha, 365 days interval, Minimum water volume: 200 L/ha						
Routes of exposure	**75th centile (mg/kg bw/day)**	**in % of AOEL[1] (RVNAS)**	**Mean (mg/kg bw/day)**	**75th centile (mg/kg bw/day)**	**in % of AOEL[1] (RVNAS)**	**Mean (mg/kg bw/day)**
Spray drift[3] (refined)[4]	0.000345	3.45	0.00027	0.000583	5.83	0.000448
Vapour (measured)	0.0000108	0.108	0.0000108	0.0000502	0.502	0.0000502
Surface deposits (acc. to EFSA)	0.000424	4.24	0.000311	0.00102	10.2	0.000748
Entry into treated crops (measured DFR)[5]	0.00172	17.2	0.00137	0.00309	30.9	0.00247
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00197 (19.7%)			0.00372 (37.2%)

[1] AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 2-3 m distance
[4] Considers measured actual dermal exposure from spray drift adjusted to BREAM2 default drift values
[5] Measured DFR = 0.689

Table 50: Bystander and resident exposure, prothioconazole-desthio, Cereals, considering revised default spray drift values from BREAM2

Substance	PTZ-Desthio	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.141 kg a.s. /ha	**Spray dilution =** 0.705 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of > 10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = -%	**Dermal for in use dilution** = 44%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.01 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	
DFR	0.689 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.000887	% of RVNAS[1]	8.87%
	Vapour (75th percentile) mg/kg bw/day	0.0000502	% of RVNAS[1]	0.5%
	Surface deposits (75th percentile) mg/kg bw/day	0.00102	% of RVNAS[1]	10.2%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0309	% of RVNAS[1]	30.9%
	All pathways (mean) mg/kg bw/day	0.00372	% of RVNAS[1]	37.32
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.00345	% of RVNAS[1]	3.45%
	Vapour (75th percentile) mg/kg bw/day	0.0000108	% of RVNAS[1]	0.108%
	Surface deposits (75th percentile) mg/kg bw/day	0.000424	% of RVNAS[1]	4.24%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00172	% of RVNAS[1]	17.2%
	All pathways (mean) mg/kg bw/day	0.00197	% of RVNAS[1]	19.7%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Table 51: Predicted systemic exposure to prothioconazole-desthio, refined, considers measured actual dermal exposure from spray drift as determined and measured DFR data regarding entry into treated crops as well as measured vapour concentrations

	Adult[2]			Child[2]		
Outdoor, Downward spraying, Vehicle-mounted Application rate: 1 x 0.141 kg a.s./ha, 365 days interval, Minimum water volume: 200 L/ha						
Routes of exposure	**75th centile (mg/kg bw/day)**	**in % of AOEL[1] (RVNAS)**	**Mean (mg/kg bw/day)**	**75th centile (mg/kg bw/day)**	**in % of AOEL[1] (RVNAS)**	**Mean (mg/kg bw/day)**
Spray drift[3] (refined)[4]	0.000345	3.45	0.00027	0.000887	8.87	0.000789
Vapour (measured)	0.0000108	0.108	0.0000108	0.0000502	0.502	0.0000502
Surface deposits (acc. to EFSA)	0.000424	4.24	0.000311	0.00102	10.2	0.000748
Entry into treated crops (measured DFR)[5]	0.00172	17.2	0.00137	0.00309	30.9	0.00247
Sum of all pathways: measured DFR [mg/kg bw/day] of AOEL (RVNAS)			0.00214 (21.4%)			0.00497 (49.7%)

[1] AOEL (RVNAS) of prothioconazole-desthio: 0.01 mg/kg bw/day
[2] Considered bodyweight: adult = 60 kg, child = 10 kg
[3] Exposure at 2-3 m distance
[4] Considers measured actual dermal exposure from spray drift adjusted to EFSA default drift values
[5] Measured DFR = 0.689

Table 52: Bystander and resident exposure, prothioconazole-desthio, Cereals, considering revised default spray drift values from BREAM2

Substance	PTZ-Desthio	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.141 kg a.s. /ha	**Spray dilution =** 0.705 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of > 10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval** = 365 days
Percentage Absorption	Dermal for product = -%	**Dermal for in use dilution** = 44%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.01 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	
DFR	0.689 µg a.s./cm² per kg a.s./ha		DT50	30 days	

Bystander - child	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
Bystander - adult	Spray drift (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Vapour (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Surface deposits (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%
	Entry into treated crops (95th percentile) mg/kg bw/day	-	% of RVNAS[1]	-%

Resident - child	Spray drift (75th percentile) mg/kg bw/day	0.000887	% of RVNAS[1]	8.87%
	Vapour (75th percentile) mg/kg bw/day	0.0000502	% of RVNAS[1]	0.5%
	Surface deposits (75th percentile) mg/kg bw/day	0.00102	% of RVNAS[1]	10.2%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.0309	% of RVNAS[1]	30.9%
	All pathways (mean) mg/kg bw/day	0.00497	% of RVNAS[1]	49.7%
Resident - adult	Spray drift (75th percentile) mg/kg bw/day	0.00345	% of RVNAS[1]	3.45%
	Vapour (75th percentile) mg/kg bw/day	0.0000108	% of RVNAS[1]	0.108%
	Surface deposits (75th percentile) mg/kg bw/day	0.000424	% of RVNAS[1]	4.24%
	Entry into treated crops (75th percentile) mg/kg bw/day	0.00172	% of RVNAS[1]	17.2%
	All pathways (mean) mg/kg bw/day	0.00214	% of RVNAS[1]	21.4%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Details regarding the refined evaluation regarding spray drift- and vapour exposure to prothioconazole-desthio considering measured data are presented in the following

Spray drift exposure

Regarding dermal exposure to prothioconazole-desthio results from three crop and substance specific drift studies are taken into account. The results reflect the use of standard nozzles without drift reduction. Two of the studies have already been evaluated during the AIR process for Prothioconazole. In this context the UK (being the RMS at that time) indicated that the application parameters did not fully match application parameters suggested by the EFSA guidance. Therefore, an additional wind tunnel experiment has been conducted. The study has been evaluated by the current RMS Poland during the AIR process for Prothioconazole. Based on the results an adjustment factor of 1.18 was applied to the drift data to cover application parameters proposed by the EFSA guidance. The third study being conducted with the aim to reflect application parameters suggested by the EFSA guidance has recently been finalised. As not being available at that time that study was not part of the AIR process for Prothioconazole. Overall the results confirm the results obtained with the first studies. Detailed summaries of the studies are presented in Direct drift: Exposure studies

As indicated for this evaluation the tiered approach is applied. In this context it is noted that the potential dermal exposure via spray drift in terms of mL/person determined in the studies was lower than the default values proposed by the EFSA guidance as shown in the following table.

Table 53: Potential dermal exposure from spray drift [mL/person]

Person	Potential dermal exposure from direct spray drift [mL/person]			
	75th percentile		mean	
	EFSA default	Crop specific studies	EFSA default	Crop specific studies
Adult:	0.47	0.1522	0.223	0.1130
Child:	0.327	0.0822	0.180	0.0636

That is a reasonable result given that the EFSA values refer to a tier one approach designed to cover the various application conditions in the field whereas with the studies the use conditions typical for fungicide application to cereal crops are reflected. However, referring to the tiered approach for the first refinement actual dermal exposures to Prothioconazole and prothioconazole-desthio determined in the field studies are adjusted to the higher default drift values proposed by the EFSA guidance. As already indicated these default values were established at that time using the BREAModel (Bystander and Resident Exposure Assessment Model). The model has recently been updated with independent support by the HSE's Chemical Regulation Division (CRD). The drift values to estimate subchronic potential dermal exposure as suggested by BREAM2 for ground boom spray applications when using standard nozzle types are presented in the following table.

Table 54: Potential dermal exposure from spray drift [mL/person] proposed by BREAM2 concerning subchronic exposure

Person	Potential dermal exposure from spray drift [mL/person]	
	75th percentile	mean
Adult:	0.252	0.185
Child:	0.183	0.133

Hence, in addition calculations are presented which consider the drift data proposed by the more recent BREAM2. The values are still higher than the values established in the field studies. This result again is reasonable and can be attributed to the fact that the mentioned BREAM2 values are nevertheless designed to cover ground boom spray applications in the field from a worst case/general perspective whereas the drift studies reflect a more specific application situation, i.e. fungicide application to cereals. For more details about BREAM2 please refer to:
https://www.ssau.co.uk/bream2-calculator.

Given that with respect to spray drift exposure the measured data are most representative for the given exposure scenario and taking furthermore into consideration that maximum application rates and maximum in use concentrations relevant for BIX + FLU + PTZ EC 260 are well covered for the last refinement step the data for prothioconazole-desthio are taken into account as determined. With that approach obviously the most realistic exposure estimates are provided.

Reasonably those refinements could be applied for Prothioconazole as well. However, as for the current evaluation it will not have a significant impact as far as the overall outcome of the risk assessment is concerned that step was not applied but could be followed up with if deemed necessary.

Concerning inhalation exposure to prothioconazole-desthio via spray drift the respective default values proposed by EFSA and BREAM2 (see Table 54) are applied together with the worst case assumption of 100% conversion. Detailed summaries of the exposure studies used for the refinements are presented in Spray drift revised

Detailed exposure calculations concerning spray drift exposure to the conversion product prothioconazole-desthio considering measurement of exposure are presented in the following.

Spray drift revised

Table 55: Resident spray drift exposure, Prothioconazole-desthio, Cereals, considering measured results for spray drift exposure but adjusted to the default drift values proposed by EFSA

Parameter	Unit	Adult Parametric 75th percentile	Adult mean	Child Parametric 75th percentile	Child mean
Dermal exposure (prothioconazole-desthio (PTZ-desthio) measured adjusted to EFSA default drift values)					
Potential dermal					
EFSA default	mL/person	0.47	0.385	0.327	0.268
measured	mL/person	0.1522	0.1130	0.0822	0.0636
Adjustment factor		3.1	2.0	4.0	2.8
Actual PTZ-desthio measured	mg/person	0.0466	0.0364	0.0194	0.0172
Actual PTZ-desthio measured adjusted	mg/person	0.144	0.0718	0.0772	0.0487
	mg/kg bw	0.00240	0.00120	0.00772	0.00487
Dermal absorption	%	44			
Systemic dose by dermal route	**mg/kg bw**	**0.00106**	**0.000528**	**0.00340**	**0.00214**
Inhalation exposure (EFSA default approach)					
Potential inhalation (EFSA default)	mL/person	0.0001	0.00009	0.00022	0.00017
In use concentration	mg/mL	0.765			
Potential inhalation exposure	mg/person	0.00017	0.000153	0.000374	0.000289
	mg/kg bw/day	0.000003	0.000003	0.000037	0.000029
Inhalation absorption	%	100			
Systemic dose by inhalation	**mg/kg bw**	**0.000001**	**0.000001**	**0.000015**	**0.000012**
Total systemic dose	**mg/kg bw**	**0.00106**	**0.000531**	**0.00343**	**0.00217**
%AOEL	**0.01 mg/kg bw**	**11**	**5.3**	**34**	**22**

1): Considers maximum Prothioconazole in use concentration of 0.78 mg/mL and molecular adjustment factor of 0.9066

With the following table detailed calculations concerning exposure to prothioconazole-desthio via spray drift considered measured data but adjusted to the default drift values proposed by BREAM2 are presented.

Table 56: Resident spray drift exposure, Prothioconazole-desthio, Cereals, considering measured results for spray drift exposure but adjusted to the default drift values proposed by BREAM2

Parameter	Unit	Adult		Child	
		Parametric 75th percentile	mean	Parametric 75th percentile	mean
Dermal exposure (prothioconazole-desthio measured adjusted to BREAM2 default drift values)					
Potential dermal					
BREAM2 default	mL/person	0.252	0.185	0.183	0.133
measured	mL/person	0.1522	0.1120	0.0822	0.0636
Adjustment factor		1.7	1.6	2.2	2.1
Actual PTZ-desthio measured	mg/person	0.0466	0.0364	0.0194	0.0172
Actual PTZ-desthio measured adjusted	mg/person	0.0772	0.0596	0.0432	0.0360
	mg/kg bw/day	0.00129	0.000993	0.00432	0.00360
Dermal absorption	%	44			
Systemic dose by dermal route	**mg/kg bw**	**0.00057**	**0.000437**	**0.0019**	**0.00158**
Inhalation exposure (BREAM2 default approach)					
Potential inhalation (BREAM2 default)	mL/person	0.000443	0.000383	0.000926	0.000721
In use concentration	mg/mL	0.705			
Potential inhalation exposure	mg/person	0.000753	0.000651	0.00157	0.00123
	mg/kg bw/day	0.000013	0.000011	0.000157	0.000123
Inhalation absorption	%	100			
Systemic dose by inhalation	**mg/kg bw**	**0.000005**	**0.000005**	**0.000065**	**0.000051**
Total systemic	**mg/kg bw**	**0.000583**	**0.000448**	**0.00206**	**0.0017**

dose					
%AOEL	**0.01 mg/kg bw**	**5.8**	**4.5**	**21**	**17**

1): Considers maximum Prothioconazole in use concentration of 0.78 mg/mL and molecular adjustment factor of 0.9066

With the following table detailed calculations concerning exposure to prothioconazole-desthio via spray drift considered measured data as determined in the crop and substance specific study are presented.

Table 57: Resident spray drift exposure, Prothioconazole-desthio, Cereals, considering measured results for spray drift exposure not adjusted to default drift values

Parameter	**Unit**	**Adult Parametric 75th percentile**	**mean**	**Child Parametric 75th percentile**	**mean**
Actual PTZ-desthio measured	mg/person	0.0466	0.0364	0.0194	0.0172
	mg/kg bw	0.00777	0.00607	0.00194	0.00172
Dermal absorption	%	44			
Systemic dose by dermal route	**mg/kg bw**	**0.000342**	**0.000267**	**0.00085**	**0.00076**
Inhalation exposure (EFSA default approach)					
Potential inhalation (EFSA default)	mL/person	0.0001	0.00009	0.00022	0.00017
In use concentration	mg/mL	0.705[1)]			
Potential inhalation exposure	mg/person	0.00017	0.000153	0.000374	0.000289
	mg/kg bw/day	0.000003	0.000003	0.000037	0.000029
Inhalation absorption	%	100			
Systemic dose by inhalation	**mg/kg bw**	**0.000001**	**0.000001**	**0.000015**	**0.000012**
Total systemic dose	**mg/kg bw**	**0.000345**	**0.00027**	**0.000887**	**0.000789**
%AOEL	**0.01 mg/kg bw**	**3.5**	**2.3**	**8.9**	**7.9**

1): Considers maximum Prothioconazole in use concentration of 0.78 mg/mL and molecular adjustment factor of 0.9066

Vapour exposure

Refinement of the exposure calculations for prothioconazole-desthio are conducted based on measured vapour concentrations. In a substance and crop specific field study the concentration of prothioconazole-desthio in the air in a 48 hours period was measured following the application of PTZ+SPX+TBZ EC 425 in a rate of 1 L/ha. A summary of the vapour study is presented in chapter Vapour: Exposure study for Prothioconazole-desthio. It is noted that the application rate of prothioconazole in the study was 53 g a.s./ha and thus lower compared to the intended rate of BIX + FLU + PTZ EC 260 i.e. 156 g a.s./ha. Thus, following a conservative approach values are corrected accordingly for the higher application rate. As surrogate value for the resident exposure estimations the 75th percentile of the 24 hour time weighted average concentration of prothioconazole-desthio is assumed, i.e. 16 ng/m³.

16 ng/m³ * (156 g a.s./ha / 53 g a.s./ha) = 47 ng/m³ when adjusted to the higher application rate.

Considering the relevant default breathing rates proposed by EFSA, exposure by vapour considering measured vapour exposure is calculated as follows:

Systemic exposure [mg a.s./day]

$$Vapour\ [mg\ a.s./day] = Air\ conc.\ [mg\ a.s./m^3] * breathing\ rate\ [m^3/day/kg] * body\ weight\ [kg]$$

where:	Air conc.		0.0000560 mg/m³
	Breathing rate	Child	1.07 m³/day/kg (10.7 m³/day/child 10 kg)
		Adult	0.23 m³/day/kg (13.8 m³/day/adult 60 kg)
	Body weight	Child	10 kg
		Adult	60 kg

$Vapour_{Child}$ (mg /day) = 0.000047 mg/m³ x 1.07 m³/day x 10 kg
= 0.000502 mg /day

$Vapour_{Adult}$ (mg /day) = 0.000047 mg/m³ x 0.23 m³/day x 60 kg
= 0.000649 mg/ day

Systemic exposure [mg a.s./kg bw/day]

$$Vapour\ [mg\ a.s./kg\ bw/day] = Vapour\ [mg\ a.s./day] / body\ weight\ [kg]$$

$Vapour_{child}$ = 0.000502 mg a.s./day / 10 kg
= 0.0000502 mg a.s./kg bw/day

$Vapour_{adult}$ = 0.000649 mg a.s./day / 60 kg
= 0.0000108 mg a.s./kg bw/day

Direct drift: Exposure studies - prothioconazole, prothioconazole-desthio (KCP 7.2.2.2)

From 2012 until 2020, Bayer conducted five studies with Prothioconazole-containing products to determine the exposure of persons (adults and children) via direct drift during ground boom application. The studies were summarized in the following summary report:

Comments of zRMS:	Comment on study; acceptable or not; deficiencies, corrections, according to recent guidelines or not, used in evaluation or only as additional information

Data Point:	KCP 7.2.2.2/08
Report Author:	[redacted]
Report Year:	2020
Report Title:	Bystander drift studies on the dermal exposure to prothioconazole and its main metabolite, prothioconazole-desthio using standard and drift reducing nozzles.
Report No:	M-682712-03-1
Document No:	M-682712-03-1
Guideline(s) followed in study:	None
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	not applicable
Acceptability/Reliability:	Yes

Introduction:
The drift studies detailed in this report were designed to quantify by means of passive dosimetry the dermal and inhalation exposure of adult and child bystanders to prothioconazole (PTZ) and its main metabolite prothioconazole-desthio (PTZ-desthio) during the application of PTZ-containing products. The design of Study 1 and 3 aimed to mimic conditions used by the majority of commercial cereal growers i.e. reflecting the application equipment (e.g. standard nozzles), test site, and other experimental conditions. Since the first study, recommendations were made to alter the study design to ensure that different exposure conditions were considered.

One of the conditions tested was the type of nozzle used for spraying; therefore, this report also addresses this aspect. An additional wind tunnel study (Study 6) was conducted to establish the difference in drift relevant to bystander exposure from a standard (Teejet XR110 03 VP) nozzle at 1.3 bar and 9 km/h (used in Studies 1 and 3) and a standard flat fan 110 03 nozzle (Hypro) at 3.0 bar (used in Study 4). This was requested during the Annex I Renewal process of prothioconazole to compare the drift results from both studies with EFSA's tier 1 default assumptions. In the wind tunnel study, droplet size distribution was measured using laser diffraction and spray drift was measured using wind tunnel measurements. The results indicate that a validation factor of 1.18 could be applied to values from Studies 1 and 3 to make them equivalent to the values from Study 4. The request to make the adjustment is detailed in a renewal assessment report (to be published by EFSA). Of note, several values for dermal exposure in Study 1 and 2 were corrected for prothioconazole-desthio field spike recoveries since these fell marginally below 95%. Since the conditions of Studies 1, 3 and 4 were similar, the values for dermal exposure using standard nozzles were pooled.

Studies 2 and 5 used drift reduction nozzles; therefore, the resulting dermal exposure values were not adjusted for the wind tunnel value. Of note, none of the values for dermal exposure in Studies 2 and 5 were corrected for field spike recoveries since these fell above 95%. Since the conditions of Studies 2 and 5 were similar, the values for dermal exposure using drift reduction nozzles were pooled.

For calculation of the summary statistics for PTZ, PTZ-desthio and total prothioconazole-equivalents (sum of PTZ and PTZ-desthio), only exposure values for mannequins positioned 2 meters from the zero line were considered, based on the EFSA guidance (EFSA Journal 2014;12(10):3874). This concludes that 2 meters represents a realistic worst-case distance. Summaries comparing the potential (naked bystander) and actual (T-Shirt/shorts) dermal exposure of PTZ and/or PTZ-desthio using standard and drift reducing nozzles are shown in Table A-57 to Table A-60.

According EFSA recommendations, the use of drift nozzles should result in a 50% reduction in drift (EFSA Journal 2014;12(10):3874). Therefore, in study 2 and 5, nozzles were used that are classified to have 50% drift reduction at the applied parameters. The results shown in Table A-57 to Table A-60 show that drift of PTZ and total PTZ equivalents was actually reduced by 61% to 75% by using drift reducing nozzles (Lechler IDKN 120-03) compared to using standard nozzles (TeeJet XR 110 03 or HYPRO F110-03).

In conclusion, data from the studies presented were pooled to reflect potential and actual exposure to PTZ and total PTZ equivalents from standard and drift-reducing nozzles. These data demonstrated that the drift reduction was 61% to 75% and exceeded the EFSA recommended value of 50%.

Table 58: Overview of five bystander field studies conducted.

	[redacted] 2015a	[redacted] 2015b	[redacted], 2015	[redacted] *et al.* 2020a	[redacted] *et al.* 2020b
Hereinafter referred to	**Study 1**	**Study 2**	**Study 3**	**Study 4**	**Study 5**
Study ID	**P 666 12 1700**	**P 666 12 1701**	**P 666 15 1700**	**P 666 19 1701**	**P666-19-1702**
Document ID	M-510333-01-1	M-510345-01-1	M-536654-02-1	M-691458-01-1	M-691460-01-1
Study title	Exposure of bystanders / residents to spiroxamine and prothioconazole from spray applications with PTZ+SPX EC 460 (160+300) in cereals using standard spray nozzles	Exposure of bystanders / residents to spiroxamine and prothioconazole from spray applications with PTZ+SPX EC 460 (160+300) in cereals using drift reducing spray nozzles	Dermal exposure of bystanders / residents to prothioconazole and its main metabolite prothioconazole-desthio from tractor mounted trailed boom sprayers with BIX+PTZ EC 225 (75 + 150) in cereals	Dermal exposure of bystanders / residents to prothioconazole and its metabolite prothioconazole-desthio from tractor mounted / trailed boom sprayers equipped with standard spray nozzles with BIX+PTZ EC 225 (75 + 150) in cereals	Dermal exposure of bystanders / residents to prothioconazole and its metabolite prothioconazole-desthio from tractor mounted/trailed boom sprayers equipped with drift reducing nozzles with BIX+PTZ EC 225 (75 + 150) in cereals
Date sprayed	May 2012	May 2012	May 2015	April 2019	April 2019
Report completion date	10/02/2015	10/02/2015	14/10/2015	2020 (draft)	2020 (draft)
No of total replicates	18 (9 adults and 9 children)	18 (9 adults and 9 children)	20 (10 adult + 10 child)	20 (10 adult + 10 child)	20 (10 adult + 10 child)
No of replicates at 2m distance	6 (3 adults and 3 children)	6 (3 adults and 3 children)	10 (5 adults and 5 children)	20 (10 adults + 10 children)	20 (10 adults + 10 children)
Crop	winter wheat late BBCH 55 height 60 cm	winter wheat late BBCH 55, height 60 cm	winter wheat late BBCH 56, height 60 cm	winter wheat BBCH 31-32, height 30 cm	winter wheat BBCH 31-32, height 30 cm
Average Wind speed	Av = 2.3 m/s measured at 2 m above the ground	2.3 m/sec measured at 2 m above the ground	3.8 m/sec measured at 2 m above the ground	3.7-4.4 m/sec measured at 2 m above the ground	2.8-3.5 m/sec measured at 2 m above the ground
Boom width	28 m	28 m	18 m	36 m	36 m

	[redacted] 2015a	[redacted] 2015b	[redacted], 2015	[redacted] *et al.* 2020a	[redacted] *et al.* 2020b
Boom height above ground	1.1 m (0.5 m above canopy height of 0.6 m)	1.1 m (0.5 m above canopy height of 0.6 m)	1.1 m (0.5 m above canopy height of 0.6 m)	1.05 m (0.75 m above canopy height of 0.3 m)	1.05 m (0.75 m above canopy height of 0.3 m)
Boom height above canopy	50 cm	50 cm	50 cm	75 cm	75 cm
Spray swath	a single spray of 1 swath covering 100 m x 28 m	a single spray of 1 swath covering 100 m x 28 m	a single spray of 2 swaths covering 100 m x 36 m	a single spray of 2 swaths covering 130 m x 72 m	a single spray of 2 swaths covering 130 m x 72 m
Distances from zero line	2, 5 and 8 m	2, 5 and 8 m	2 and 5 m	2 m	2 m
Test item	Input EC 460	Input EC 460	BIX+PTZ EC 225	BIX+PTZ EC 225	BIX+PTZ EC 225
Nozzle	standard spray nozzles (TeeJet XR 110 03)	drift reducing nozzles (50%) (Lechler IDKN 120-03)	standard spray nozzles (TeeJet XR 110 03)	EFSA standard nozzles (HYPRO F110-03)	drift reducing nozzles (50%) (Lechler IDKN 120-03)
No. Nozzles	56	56	36	72	72
Nozzle pressure	1.5 bar	1.5 bar	1.3 bar	2.1 bar	3 bar
Driving speed	10 km/h	10 km/h	9 km/h	12.2 km/h	12.6 km/h
Area sprayed	0.28 ha	0.28 ha	0.36 ha	0.936 ha	0.936 ha
Spray volume	100 L/ha	100 L/ha	100 L/ha	114 L/ha	114 L/ha
Dose rate (a.s./ha)	200 g PTZ/ha	200 g PTZ/ha	187.50 g PTZ/ha	187.53 g PTZ/ha	187.5 g PTZ/ha
Dose rate (product/ha)	1.25 L/ha	1.25 L/ha	1.25 L/ha	1.25 L/ha	1.25 L/ha
Spray concentration	200 g/ha / 100 L/ha = 2.00 mg/mL	200 g/ha / 100 L/ha = 2.00 mg/mL	187.5 g/ha / 100 L/ha = 1.875 mg/mL	187.5 g/ha / 114 L/ha = 1.64 mg/mL	187.5 g/ha / 114 L/ha = 1.64 mg/mL

Table 59: **Pooled values for potential dermal exposure (naked bystander) to Prothioconazole and to prothioconazole-desthio of adults and children positioned 2 meters from the zero line.**

Statistical parameter	Potential exposure [mg/person]							
	Standard nozzles				Drift reducing nozzles			
	Prothioconazole		prothioconazole-desthio		Prothioconazole		prothioconazole-desthio	
	Adult	Child	Adult	Child	Adult	Child	Adult	Child
Number of replicates	18	18	18	18	13	13	13	13
Mean	0.1357	0.0790	0.0585	0.0290	0.0344	0.0250	0.0261	0.0149
SD	0.0630	0.0450	0.0265	0.0167	0.0291	0.0223	0.0232	0.0134
Maximum	0.2590	0.2016	0.1332	0.0823	0.1061	0.0651	0.0859	0.0399
Empirical 75th percentile	0.1725	0.1008	0.0725	0.0309	0.0358	0.0307	0.0267	0.0175
Empirical 95th percentile	0.2331	0.1476	0.0853	0.0480	0.0916	0.0621	0.0716	0.0395
Parametric 75th percentile	0.1775	0.1052	0.0743	0.0330	0.0397	0.0454	0.0287	0.0247
Parametric 95th percentile	0.2590	0.2016	0.1332	0.0823	0.1061	0.0651	0.0859	0.0399

Table 60: **Pooled values for actual dermal exposure (representing the lightly dressed resident wearing only shorts and t-shirt) to Prothioconazole and to prothioconazole-desthio of adults and children positioned 2 meters from the zero line.**

Statistical parameter	Potential exposure [mg/person]							
	Standard nozzles				Drift reducing nozzles			
	Prothioconazole		prothioconazole-desthio		Prothioconazole		prothioconazole-desthio	
	Adult	Child	Adult	Child	Adult	Child	Adult	Child
Number of replicates	18	18	18	18	13	13	13	13
Mean	0.0761	0.0448	**0.0364**	**0.0172**	0.0248	0.0155	0.0165	0.0090
SD	0.0362	0.0261	0.0169	0.0094	0.0210	0.0144	0.0147	0.0080
Maximum	0.1416	0.1140	0.0833	0.0465	0.0780	0.0460	0.0575	0.0259
Empirical 75th percentile	0.0949	0.0546	0.0441	0.0191	0.0309	0.0197	0.0180	0.0098
Empirical 95th percentile	0.1336	0.0845	0.0567	0.0290	0.0632	0.0445	0.0426	0.0237
Parametric 75th percentile	0.0968	0.0607	**0.0466**	**0.0194**	0.0330	0.0202	0.0193	0.0136
Parametric 95th percentile	0.1416	0.1100	0.0833	0.0465	0.0780	0.0460	0.0575	0.0259

Values for standard nozzles are from studies 1, 3 and 4 and values for drift reduction nozzles are from studies 2 and 5. Replicates and their associated statistical parameters are shown in the Appendix, Table A1.
All values in studies 1 and 3 were corrected with the validation factor of 1.18 derived from the wind tunnel experiments described in Section 8.
Several values in Studies 1 and 2 were corrected for recovery based on the field spike recoveries.

Table 61: Potential dermal exposure to total prothioconazole equivalents (prothioconazole+ prothioconazole-desthio) of adults and children positioned 2 meters from the zero line from studies 2 and 5, in which drift reduction nozzles were used.
(Values in bold indicate the values that are considered to estimate resident exposure to prothioconazole-desthio via spray drift)

Statistical parameter	Standard nozzles				Drift reducing nozzles			
	mg/person		mL/person		mg/person		mL/person	
	Adult	Child	Adult	Child	Adult	Child	Adult	Child
Number of replicates	18	18	18	18	13	13	13	13
Mean	0.2002	0.1110	0.1132	0.0637	0.0632	0.0414	0.0378	0.0250
SD	0.0872	0.0621	0.0464	0.0372	0.0544	0.0369	0.0335	0.0228
Maximum	0.3345	0.2924	0.1777	0.1783	0.2008	0.1091	0.1225	0.0665
Empirical 75th percentile	0.2461	0.1463	0.1482	0.0805	0.0653	0.0500	0.0398	0.0305
Empirical 95th percentile	0.3336	0.1876	0.1688	0.1066	0.1704	0.1057	0.1039	0.0645
Parametric 75th percentile	0.2509	0.1511	**0.1526**	**0.0823**	0.0713	0.0726	0.0434	0.0443
Parametric 95th percentile	0.3345	0.2924	0.1777	0.1783	0.2008	0.1091	0.1225	0.0665

Table 62: **Dermal exposure to total prothioconazole equivalents (prothioconazole+ prothioconazole-desthio) of adults and children positioned 2 meters from the zero line from studies 2 and 5, in which drift reduction nozzles were used.**

Statistical parameter	Standard nozzles				Drift reducing nozzles			
	mg/person		mL/person		mg/person		mL/person	
	Adult	Child	Adult	Child	Adult	Child	Adult	Child
Number of replicates	18	18	18	18	13	13	13	13
Mean	0.1163	0.0637	0.0661	0.0369	0.0430	0.0254	0.0257	0.0153
SD	0.0510	0.0355	0.0284	0.0217	0.0371	0.0230	0.0228	0.0141
Maximum	0.1896	0.1623	0.1109	0.0990	0.1414	0.0721	0.0862	0.0439
Empirical 75th percentile	0.1502	0.0794	0.0916	0.0484	0.0508	0.0305	0.0309	0.0186
Empirical 95th percentile	0.1849	0.1103	0.1025	0.0672	0.1102	0.0712	0.0672	0.0434
Parametric 75th percentile	0.1586	0.0862	0.0920	0.0507	0.0542	0.0351	0.0331	0.0214
Parametric 95th percentile	0.1896	0.1623	0.1109	0.0990	0.1414	0.0721	0.0862	0.0439

The following studies were used in this report:

Comments of zRMS:	Comment on study; acceptable or not, deficiencies, corrections, according to recent guidelines or not, used in evaluation or only as additional information

Data Point:	KCP 7.2.2.2/07
Report Author:	[redacted]
Report Year:	2015
Report Title:	Exposure of bystanders / residents to spiroxamine and prothioconazole from spray applications with Input in cereals using standard spray nozzles
Report No:	MR-14/075
Document No:	M-510333-01-1
Guideline(s) followed in study:	OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Series on Testing and Assessment No. 9, 1997 Equipment for crop protection - Methods for field measurement of spray drift, ISO 22866:2005(E)
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Data Point:	KCP 7.2.2.2/06
Report Author:	[redacted]
Report Year:	2015
Report Title:	Exposure of bystanders / residents to spiroxamine and prothioconazole from spray application with Input in cereals using drift reducing spray nozzles
Report No:	MR-14/076
Document No:	M-510345-01-1
Guideline(s) followed in study:	Special designed study in accordance with the Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Series on Testing and Assessment No. 9, OECD/GD(97)148 Equipment for crop protection - Methods for field measurement of spray drift, ISO 22866:2005(E)
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Data Point:	KCP 7.2.2.2/05
Report Author:	[redacted]
Report Year:	2015
Report Title:	Amendment no.1 to final report of study ID: P-666-15-1700 - Dermal exposure of bystanders / residents to prothioconazole and its main metabolite prothioconazole-desthio from tractor mounted/trailed boom sprayers with Aviator XPRO EC 225 in cereals
Report No:	P666151700
Document No:	M-536654-02-1
Guideline(s) followed in study:	OECD Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Series on Testing and Assessment No. 9, 1997 Equipment for crop protection - Methods for field measurement of spray drift, ISO 22866:2005(E)
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Data Point:	KCP 7.2.2.2/04
Report Author:	[redacted]
Report Year:	2020
Report Title:	Dermal exposure of Bystanders/residents to prothioconazole and its metabolite prothioconazole-desthio from tractor mounted/trailed boom sprayers equipped with standard spray nozzles with BIX+PTZ EC 225 (75 + 150) in cereals
Report No:	P 666 19 1701
Document No:	M-691458-01-1
Guideline(s) followed in study:	Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Series on Testing and Assessment No. 9, OECD/GD (97)148 and Equipment for crop protection - Methods for field measurement of spray drift, ISO 22866:2005(E)
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Data Point:	KCP 7.2.2.2/03
Report Author:	[redacted]
Report Year:	2020
Report Title:	Dermal exposure of Bystanders/Residents to Prothioconazole and its metabolite prothioconazole-desthio from tractor mounted/trailed boom sprayers equipped with drift reducing nozzles with BIX+PTZ EC 225 (75 + 150) in cereals
Report No:	P 666 19 1702
Document No:	M-691460-01-1
Guideline(s) followed in study:	Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Series on Testing and Assessment No. 9, OECD/GD (97)148 and Equipment for crop protection - Methods for field measurement of spray drift, ISO 22866:2005(E)
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

In addition, the following wind tunnel study was used to derive a validation factor:

Data Point:	KCP 7.2.2.2/02
Report Author:	[redacted]
Report Year:	2018
Report Title:	Comparison of drift potential for two nozzle/pressure/forward speed combinations
Report No:	M-642728-01-1
Document No:	M-642728-01-1
Guideline(s) followed in study:	None
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	No, not conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

Vapour: Exposure study for Prothioconazole-desthio (KCP 7.2.2.2)

The vapour exposure study was conducted under GLP by Bayer AG Crop Science division in Germany. The study was designed to cover use parameters which are relevant for ground boom spray applications in the field. The study design was similar to those studies, which served as the basis to set the currently used EFSA default values (1µg/m³ for low volatile compounds (Siebers *et al.* 2003)[3], 15 µg/m³ for moderate volatile compounds (Californian department of Pesticide regulation, 2002)[4].
The minimum water rate of 150 L/ha was applied.
A summary of the study is provided below.

Comments of zRMS:	Comment on study; acceptable or not; deficiencies, corrections, according to recent guidelines or not, used in evaluation or only as additional information

Reference:	**KCP 7.2.2.2/08**
Title:	Inhalation exposure of bystanders/residents to spiroxamine, tebuconazole and prothioconazole-desthio via vapour following tractor mounted/trailed boom sprayer application of PTZ+SPX+TBZ EC 425 in cereals
Report:	[redacted]
Authority registration No:	
Guideline(s):	Guidance Document for the Conduct of Studies of Occupational Exposure to Pesticides During Agricultural Application, Series on Testing and Assessment No. 9, OECD/GD(97)148 Equipment for crop protection - Methods for field measurement of spray drift, ISO 22866:2005(E)
Deviations:	None
GLP/GEP:	Yes
Acceptability:	
Duplication (if vertebrate study):	

I. Material and methods

This report summarises the results of field testing conducted in Germany to determine the inhalation exposure of bystanders/residents via vapour to spiroxamine (SPX), tebuconazole (TBZ) and prothioconazole-desthio (PTZ-desthio), which is the main metabolite of prothioconazole (PTZ) during a period of 48 hours after spraying a winter barley field with PTZ+SPX+TBZ EC 425. PTZ+SPX+TBZ EC 425 is formulated as an emulsifiable concentrate comprising the active ingredients PTZ (53 g/L), SPX (224 g/L) and TBZ (148 g/L). The spray application was performed with a commercial field crop boom sprayer with 36 m boom width. PTZ+SPX+TBZ EC 425 was applied with the label specific rate of 1 L/ha (nominal 53 g a.s./ha PTZ, 224 g a.s./ha SPX and 148 g a.s/ha PTZ) using standard spray nozzles (Teejet XR 110-04). Water from local sources was used to make up the spray mixture. A water volume of 150 L/ha was applied.
Spray application with PTZ+SPX+TBZ EC 425 was performed in inhomogeneous winter barley (BBCH 60 - 75, height 90 cm) grown on commercial agricultural land around Bayer AG, Crop Science Division's headquarter in D-40789 Monheim, Alfred-Nobel-Str. 50, Germany. A 0.72 ha field was selected that was surrounded by a vegetation free area of at least three meters on which the sampling equipment was positioned.

[3] Siebers JN, Binner R and Wittich KP, 2003. Investigation on downwind short-range transport of pesticides after application in agricultural crops. Chemosphere, 51, 397–407.
[4] Californian Department of Pesticide regulation, Toxic Air Contaminant Program Monitoring Reports 2002. Available at http://www.cdpr.ca.gov/docs/emon/pubs/tac/tacstdys.htm

In total 12 air sampling pumps equipped with XAD tubes were positioned at 2 m distances to the field border in regular distances around the treated field. The XAD tubes were fixed at suitable stands in a height of 50 cm above the canopy and connected with the pumps via flexible tubes. The study design was similar to those studies, which served as the basis to set the currently used EFSA default values. An illustration of the study design is presented in the following figure:

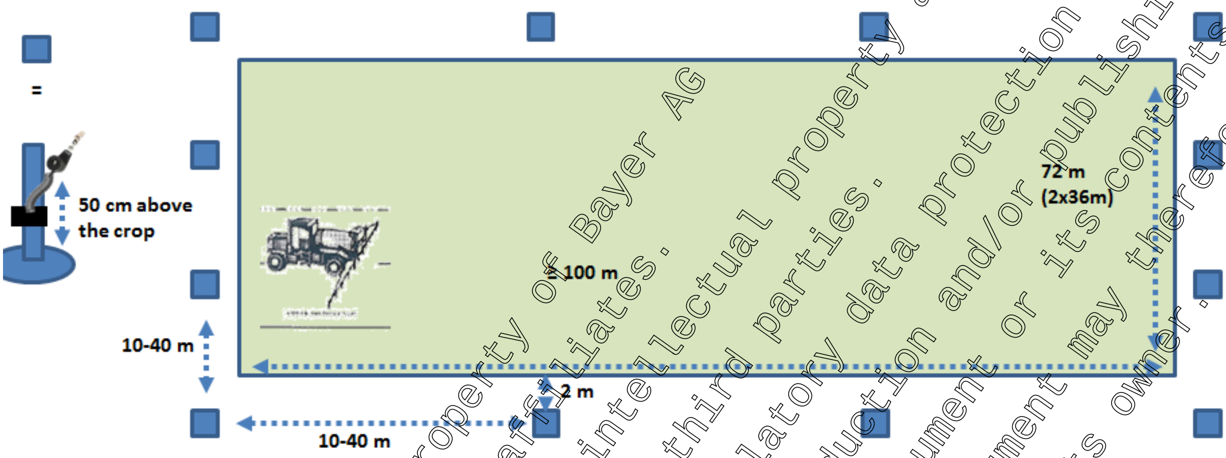


Figure A1: **Study design**

The pumps were started after the spraying of the field was finished and exposure via direct drift of the spray was not expected anymore (approx. 20 minutes after spraying).
The air sampling was performed over a period of 48 hours after the spray event periodically. During the sampling period the air sampling pumps were replaced at each sampling event to avoid interruption of measurement due to empty batteries. Following the spray event the XAD tubes were changed after 2 hours, 8 hours, 16 hours, 24 hours, 32 hours, 40 hours, 48 hours. The flow rate of the pumps (1 L/minute) was checked whenever pump and/or XAD tube was changed. If necessary the pumps were re-calibrated to the required flow rate.
In parallel the study personnel fortified sets of unexposed air sampling tubes with known quantities of TBZ, the metabolite PTZ-desthio and SPX. The XAD tubes were connected to the air sampling pump running under ambient conditions for 8 hours. All field recovery samples were placed in a location free from possible contamination. At the end of the exposure monitoring the samples were treated and processed as described for the test samples. All samples were stored at approx. – 20° C prior to extraction and analysis.
Residues of TBZ, PTZ-desthio and SPX were extracted from samples using LC/MS/MS detection system. Spiroxamine was determined as the sum of its separately quantified isomers A + B and its potential oxidation product Spiroxamine-N-oxide.
The Limit of Quantification (LOQ) for residues of TBZ, PTZ desthio and SPX were 0.01 µg/m³ (for Spiroxamine: sum of A and B isomers, and Spiroxamine-N-oxide).
The amount of residues found on each XAD tube is used to calculate the average concentration of the substance in the air during the measuring period of a XAD tube and cumulative for each sampling position over the whole trial.

II. Findings

Field recoveries which were set up during the study showed that the residues of PTZ-desthio and TBZ were stable. The mean recovery was 89% for PTZ-desthio with a RSD of 9.2%. The mean recovery for TBZ was 93% with a relative standard deviation of 8.4%
The mean recovery from the matrices fortified in the field for SPX (A and B isomers, and Spiroxamine-N-oxide) was lower: 55% for SPX A-isomer with a RSD of 9.8%, 51% for SPX B-isomer with a RSD of 11%, and 14% for SPX N-oxide after spiking with spiroxamine with a RSD of

24.7%. The measured residues for the SPX (sum of A and B isomers, and Spiroxamine-N-oxide) were therefore corrected for a recovery rate of 65%.
The measured residues at the sampling positions are presented in the tables below.

Table 63: Residues of spiroxamine (SPX) in XAD tubes (sum of A and B isomers, and Spiroxamine-N-oxide corrected for molar ratio) in ng a.s./XAD tube, results are corrected for field recovery 65%

Time after appl. [h]	Sampling duration [h]	ng a.s./XAD tube											
		1	2	3	4	5	6	7	8	9	10	11	12
2	2	7.2	7.20	9.19	7.20	13.06	15.63	16.60	46.27	51.20	28.84	30.49	28.32
8	6	15.29	7.20 *	8.89	7.20	7.20	7.20	7.20	12.53	21.37	7.20* *	53.66	41.66
16	8	26.90	58.10	66.15	31.38	64.06	58.44	38.61	60.75	57.00	33.79	44.53	49.66
24	8	7.20	7.20	16.52	7.20	7.20	7.20	7.20	14.41	14.17	7.20	11.55	8.94
32	8	7.20	7.20	7.20	7.20	7.20	11.32	7.20	11.98	7.20	7.20	11.75	11.03
40	8	7.20	13.73	19.12	10.89	19.61	19.97	28.84	31.39	33.09	18.12	16.16	15.19
48	8	7.20	7.20	7.20	7.20	7.20	7.20	7.20	7.20	13.67	7.20	7.20	7.20

* air sampling pump was not running at the time of sampling, display showed no run time

** air sampling pump was not running at the time of sampling, display showed run time of 247 minutes

Table 64: Residues of tebuconazole (TBZ) in XAD tubes in ng a.s./XAD tube

Time after appl.[h]	Sampling duration [h]	ng a.s./XAD tube											
		1	2	3	4	5	6	7	8	9	10	11	12
2	2	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40
8	6	2.40	2.40*	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40**	2.40	2.40
16	8	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40
24	8	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40
32	8	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40
40	8	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40
48	8	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40

* air sampling pump was not running at the time of sampling, display showed no run time

** air sampling pump was not running at the time of sampling, display showed run time of 247 minutes

Table 65: Residues of prothioconazole-desthio (PTZ-desthio) in XAD tubes ng a.s./XAD tube

Time after appl.[h]	Sampling duration [h]	ng a.s./XAD tube											
		1	2	3	4	5	6	7	8	9	10	11	12
2	2	2.40	2.40	2.40	2.40	2.40	2.40	2.40	6.16	8.21	5.77	7.46	9.18
8	6	7.54	2.40*	2.40	2.40	2.40	2.40	2.40	2.40	7.22	5.60**	19.50	13.80
16	8	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40
24	8	2.40	7.43	9.08	2.40	5.90	6.65	2.40	10.10	10.70	5.76	11.60	11.00
32	8	2.40	4.87	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	12.10	9.18
40	8	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40	2.40
48	8	2.40	2.40	2.40	2.40	6.61	2.40	2.40	2.40	7.51	2.40	2.40	2.40

* air sampling pump was not running at the time of sampling, display showed no run time
** air sampling pump was not running at the time of sampling, display showed run time of 247 minutes

Time weighted average concentrations in the air of Spiroxamine, Tebuconazole and Prothioconazole-desthio were calculated for a 24 hours period and a 48 hours sampling period considering the cumulative residue levels at each sampling location for the respective time period.

Table 66: Cumulative residues of spiroxamine (SPX), tebuconazole (TBZ) and prothioconazole-desthio (PTZ-desthio) in a 24 hours and 48 hours sampling period

Time after appl. [h]	Sample position											
	1	2	3	4	5	6	7	8	9	10	11	12
	Spiroxamine ng a.s./sampling position											
24	56.58	79.69	100.76	52.97	91.51	88.46	69.60	133.97	143.73	77.02	140.23	128.59
48	78.17	107.82	134.26	78.25	125.51	126.95	112.84	184.53	197.69	109.53	175.34	162.00
	Tebuconazole sampling position											
24	9.60	9.60	9.60	9.60	9.60	9.60	9.60	9.60	9.60	9.60	9.60	9.60
48	16.80	16.80	16.80	16.80	16.80	16.80	16.80	16.80	16.80	16.80	16.80	16.80
	Prothioconazole-desthio sampling position											
24	14.74	14.63	16.28	9.60	13.10	13.85	9.60	21.06	28.53	19.53	40.96	36.38
48	21.94	24.30	23.48	16.80	24.51	21.05	16.80	28.26	40.84	26.73	57.86	50.36

Table 67: Average concentration of spiroxamine (sum of A and B isomers, and Spiroxamine-N-oxide corrected for molar ratio) in the air at each sampling position in a 24 hours period and a 48 hours period after the application (time weighted average)

Time after appl. [h]	m³ air (cumulative)	Sample position											
		1	2	3	4	5	6	7	8	9	10	11	12
		Spiroxamine ng a.s./m³ air											
24	1.44	39.29	55.34	69.97	36.78	63.55	61.42	48.33	93.03	99.81	53.49	97.38	89.30
48	2.88	27.14	37.44	46.62	27.17	43.58	44.08	39.18	64.07	68.64	38.03	60.88	56.25
		Tebuconazole ng a.s./m³ air											
24	1.44	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67	6.67
48	2.88	5.83	5.83	5.83	5.83	5.83	5.83	5.83	5.83	5.83	5.83	5.83	5.83
		Prothioconazole-desthio ng a.s./m³ air											
24	1.44	10.24	10.16	11.31	6.67	9.10	9.62	6.67	14.63	19.81	13.56	**28.44**	25.26
48	2.88	7.62	8.44	8.15	5.83	8.51	7.31	5.83	9.81	14.18	9.28	20.09	17.49

III. Conclusions:

For a bystander and resident risk assessment time weighted average concentrations of the active substances are considered. An exposure duration of 24 hours is assumed. Thus, consideration of the average concentration determined for the first 24 hours following an application of the product represents conservative approach to estimate exposure of residents and bystanders to vapour following the application of a plant protection product. The 75th percentiles and 95th percentiles of the calculated time weighted average concentrations are applicable for the estimation of sub-chronic and acute exposure, respectively.

	Spiroxamine	**Tebuconazole**	**Prothioconazole-desthio**
	ng a.s./m³ air		
75th percentile	90.23	6.67	15.92
95th percentile	98.48	6.67	26.70
Defaults according to EFSA	25000	1000	1000

Accordingly, concerning exposure of residents via prothioconazole-desthio vapour a vapour concentration of 16 ng/m³ is considered (= 75th percentile value of 15.92 ng/m³ rounded to the upper end).

CP 7.2.3 Worker exposure

CP 7.2.3.1 Estimation of worker exposure

A summary of the exposure models used for the estimation of worker exposure with default DFR (= 3 µg/cm²) to the active substance(s) after entry into a previously treated area or handling a crop treated with BIX+FLU+PTZ EC 260 (65+65+130) is presented in the following table. Detailed calculations are presented in the following tables.

Table 68: Exposure models for intended uses

Critical use(s)	1.2 L / kg product/ha for Cereals
Model	*Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874*

The following table shows the crop groups with their respective transfer coefficients (TC) and task duration relevant for the estimation of worker exposure after the intended use of BIX+FLU+PTZ EC 260 (65+65+130). Worker exposures for all intended uses within the zone/ EU given in Part B, Section 0 are covered by that.

Here again it has to be mentioned that after foliar spray application of prothioconazole-containing products diluted prothioconazole can degrade to prothioconazole-desthio on plant surfaces, clothing or skin. Accordingly, although prothioconazole-desthio is not part of the formulation per se non-dietary risk assessments are always performed for prothioconazole-desthio due to its toxicological properties.

For the first tier evaluation a conservative approach was applied and the following assumptions were used in the exposure calculations for the exposure risk of workers to prothioconazole-desthio:

- For the exposure assessment to prothioconazole-desthio a 100% conversion of prothioconazole to prothioconazole-desthio is assumed. When calculating the amount of prothioconazole-desthio a conversion factor of 0.907 is applied (based on a molecular weight of 344.254 g/mol for Prothioconazole and 312.194 g/mol for prothioconazole-desthio).
- No conversion of prothioconazole to prothioconazole-desthio was considered for the exposure assessment to prothioconazole.

However, to achieve a more accurate risk evaluation the exposure assessment should always consider measured data whenever such data are available. Thus, worker exposure to prothioconazole-desthio is further assessed considering the default parameters proposed by EFSA regarding the TC and work duration but using measured DFR values for prothioconazole-desthio on cereals. Details are presented in Detailed evaluation of DFR study relied upon and Worker exposure calculations.

Table 69: Relevant parameters used for the worker exposure assessment

Crop / Crop Group	N° of applications	Interval (Days)	TC[1] (cm²/hour)	Task Duration (hours)
Cereals	1	365	1400[2]	2

[1] TC = transfer coefficients
[2] TC assuming arms, body and legs covered.

The outcome of the estimation is presented in the following tables.

Table 70: Estimated worker exposure for re-entry in Cereals

Active substance	Application rate (kg a.s./ha)	Total absorbed dose[2] (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
FLU	0.078	0.00764	153
PTZ	0.156	0.0153	7.64
BIX	0.078	0.00764	5.88
prothioconazole-desthio*	0.141	0.00872	872

[1] AOEL (RVNAS) of FLU: 0.05 mg/kg bw/day
PTZ: 0.2 mg/kg bw/day
BIX: 0.13 mg/kg bw/day
prothioconazole-desthio: 0.01 mg/kg bw/day

[2] Assuming arms, body and legs covered

* Considers Prothioconazole application rate of 0.156 kg a.s./ha, 100% conversion to prothioconazole- desthio and the molar ratio factor of 0.907 (based on a molecular weight of 344.254 g/mol for Prothioconazole and 312.194 g/mol for prothioconazole-desthio)

Conclusion

The exposure estimations carried out indicated that the acceptable worker exposure level (AOEL) will not be exceeded under conditions of intended uses and considering above mentioned personal protective equipment (PPE).
Based on the presented calculation it is demonstrated that no unacceptable risk is given with the intended use of BIX+FLU+PTZ EC 260.

CP 7.2.3.2 Measurement of worker exposure

As indicated with a higher tier approach worker exposure to prothioconazole-desthio is assessed considering the default parameters proposed by EFSA regarding the TC and work duration as already outlined in Table 69.

Concerning DFR measured values are taken into account that were determined in two crop specific studies. A maximum DFR value at the day of the second application of 0.116 µg a.s./cm² (0.125 µg/cm² when corrected for field recovery) was determined. This value can be regarded as highly conservative since the application rate of prothioconazole was higher in the study (0.2 kg a.s./ha vs. 0.156 kg a.s./ha in BIX + FLU + PTZ EC 260 as well as the number of applications (two applications in the study vs one in BIX + FLU + PTZ EC 260. The same applies for the 3 active substances in the product for details please see Table 72. The measured values corrected for field recovery are used to refine the worker exposure assessment when entering a treated field for scouting activities after the last application when the spray had dried on the leaf surface.

Refinement of generic DFR value (KCP 7.2)

A summary of the exposure models used for the estimation of worker exposure with measured DFR (default DFR: 3 µg/cm²) if available to the active substance(s) after entry into a previously treated area or handling a crop treated with BIX+FLU+PTZ EC 260 (65+65+130) is presented in the following tables.

Table 71: Exposure models for intended uses

Critical use(s)	1.2 L / kg product/ha for Cereals
Model	*Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874*

The following table shows the parameters of the used DFR studies. Worker exposures for all intended uses within the zone/ EU given in Part B, Section 0 are covered by that.

Table 72: Relevant parameters used for the worker exposure assessment

Active substance	**Crop / Crop Group**	**Application rate (kg a.s./ha)**	**N° of applications**	**Interval** (Days)	**TC**[1] (cm²/hour)	**Task Duration** (hours)	**Measured DFR** (µg/cm²/kg a.s./ha)
FLU	Cereals	0.078	1	365	1400[2]	2	0.896
PTZ	Cereals	0.156	1	365	1400[2]	2	0.51
BIX	Cereals	0.078	1	365	1400[2]	2	1.031
prothioconazole-desthio	Cereals	0.141	1	365	1400[2]	2	0.689

[1] TC = transfer coefficients
[2] TC assuming arms, body and legs covered.

The outcome of the estimation is presented in the following tables.

Table 73: Estimated worker exposure for re-entry in Cereals

Active substance	Application rate (kg a.s./ha)	DFR (µg/cm²/kg a.s./ha)	Total absorbed dose[2] (mg/kg/day)	% of systemic AOEL[1] (RVNAS)
FLU	0.078	3[3]	0.00764	15.3
		0.896[4]	0.00228	4.57
PTZ	0.156	3[3]	0.0153	7.64
		0.51[4]	0.0026	1.3
BIX	0.078	3[3]	0.00764	5.88
		1.031[4]	0.00263	2.02
prothioconazole-desthio	0.141	3[3]	0.00872	87.2
		0.689[4]	0.002	20

[1] AOEL (RVNAS) of FLU: 0.05 mg/kg bw/day
PTZ: 0.2 mg/kg bw/day
BIX: 0.13 mg/kg bw/day
PTZ-desthio: 0.01 mg/kg bw/day

[2] Assuming arms, body and legs covered

[3] Calculation with default DFR according to model

[4] Calculation with measured DFR assuming highest DFR after maximum number of applications

Conclusion

The exposure estimations carried out indicated that the acceptable worker exposure level (AOEL) will not be exceeded under conditions of intended uses and considering above mentioned personal protective equipment (PPE).

Based on the presented calculation it is demonstrated that no unacceptable risk is given with the intended use of BIX+FLU+PTZ EC 260.

Detailed evaluation of DFR study relied upon (KCP 7.2, KCP 7.2.1.1, KCP 7.2.2.1, KCP 7.2.3.1)

Data Point:	KCP 7.2.3.2/01
Report Author:	[redacted]
Report Year:	2017
Report Title:	Determination of the dislodgeable foliar residues (DFR) of BYF 00587 and AE C656948 in/on wheat after spray application of bixafen & fluopyram & prothioconazole EC 260 in the field in Belgium
Report No:	16-2908
Document No:	M-607649-01-1
Guideline(s) followed in study:	US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation
Deviations from current test guideline:	None
Previous evaluation:	Not, previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

The magnitude of the dislodgeable foliar residues (DFR) of the substances AE C656948 (FLU) and BYF 00587 (BIX) in washings from wheat leaf punches was determined after two applications with Bixafen & Fluopyram & Prothioconazole EC 260 (containing 130 g/L prothioconazole, 65 g/L AE C656948 and 65 g/L BYF 00587). Prothioconazole was not subject of the study and was not analyzed.

The study included one supervised residue trial conducted in the field in northern Europe (Belgium) during the 2016 season.

The actual application data are presented in the following table. These data reflect the intended application scheme, or, if minor deviations occurred, these were within the acceptable range.

Table 74; Application summary

Trial Number / Country	Crop	Appl. Number	Interval (days)	Growth Stage (BBCH)	Dose rate (L/ha)	Water rate (L/ha)	Appl. rate (kg a.s./ha)		
							prothioconazole	AE C656948	BYF 00587
16-2908-01 Belgium	wheat	1	-	37-39	1.5	200	0.195	0.098	0.098
		2	14	57	1.5	200	0.195	0.098	0.098
Appl. = Application; a.s. = active substance.									

Representative leaf punch samples were obtained, prepared, identified, transported and stored following the corresponding study plan and EPA OPPTS Guideline 875.2100 (1996).

Eighty leaf disks representing a total area of 200 cm² (double-sided surface) were collected out of the potential worker contact zone including upper, middle, lower, interior and exterior portions of wheat foliage after the spray application was dry, according to study schedule. The application equipment used in the study was representative for the crop, the region and the task.

Control samples were collected prior to the first application. Field fortification samples were also generated at the field test site.

Leaf discs were dislodged with a 0.01 % Aerosol OT surfactant solution yielding a total amount of 200 mL of dislodging solution. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after sample collection.

Table 75: General data

EU zone	Outdoor / Greenhouse	Leaf disk area (cm^2)	Number of leaf disks	Total surface area (Double-sided surface) (cm^2)	Dislodging solution	Amount of dislodging solution (mL)
North	outdoor	1.25	80	200	0.01% Aerosol OT surfactant in tap water	200

Sampling information is given in the report.

Table 76: Information on rainfall events during the study time

Date/Period of Time	Activity	Mean Temp. [°C]	Rainfall [mm]	Sunshine [h]
2016-05-17	Treatment, Sampling	13	8	13
2016-05-18	Sampling	14	0	12
2016-05-20	Sampling	14	0	
2016-05-24	Sampling	12	0	11
2016-05-27	Sampling	17	7	11
2016-05-31	Treatment, Sampling	15	11	-
2016-06-01	Sampling	15	12	10
2016-06-03	Sampling	14	3	12
2016-06-07	Sampling	20	22	11
2016-06-10	Sampling	17	0	15
May 2016	-	14	43	-*
June 2016		16	135	380

Climatic data recording was not conducted according to GLP. No irrigation done
*No monthly sunshine data from May available.

In order to check the performance of the method and the stability of the field samples, recovery determinations were performed from control samples individually spiked with fluopyram and bixafen during the field part. The results are presented in following tables:

Table 77: Field Spike Recovery Data for AE C656948 (fluopyram)

Crop / Sample material	FL [µg/cm^2]	Single values [%]	Mean value [%]	RSD [%]	LOQ [µg/cm^2]
wheat / leaf punch washings	0.01	88; 99;85	91	8.1	0.01
	0.1	100; 94; 90	95	5.3	
	1.0	95; 90; 96	94	3.4	
		Overall recovery (n = 9)	**93**	**5.5**	

FL = Fortification level, RSD = Relative standard deviation, LOQ = Practical limit of quantification.
These recoveries were performed during the conduct of the study 16-2908.

Table 78: Field Spike Recovery Data for BYF 00587 (bixafen)

Crop / Sample material	FL [µg/cm²]	Single values [%]	Mean value [%]	RSD [%]	LOQ [µg/cm²]
wheat / leaf punch washings	0.01	106; 111; 97	105	6.8	0.01
	0.1	107; 106; 89	101	10.0	
	1.0	96; 101;99	99	2.6	
		Overall recovery (n = 9)	**101**	**6.7**	

FL = Fortification level, RSD = Relative standard deviation, LOQ = Practical limit of quantification.
These recoveries were performed during the conduct of the study 16-2908.

Absolute (µg/cm²) DFR values fluopyram and bixafen are summarised in the following tables. No residues above the LOQ (0.01 µg/cm²) were found in the control samples. Results were not corrected for field spike recoveries.

Table 79: Dislodgeable Foliar Residue summary in/on wheat for AE C656948 (fluopyram)

Trial N° Country	DA1.T	DA2.T	Plot T1 [µg/cm²]	Plot T2 [µg/cm²]	Plot T3 [µg/cm²]	Mean residues T1-T3 [µg/cm²]
16-2908-01 Belgium	0		0.0768	0.117	0.0695	**0.0878**
	1		0.0548	0.0438	0.0583	**0.0523**
	3		0.028	0.053	0.042	**0.034**
	7		<0.01	<0.01	<0.01	**<0.01**
	10		<0.01	<0.01	<0.01	**<0.01**
	14	-0	<0.01	<0.01	<0.01	**<0.01**
		0	0.107	0.0459	0.0937	**0.0822**
		1	0.0569	0.0658	0.0459	**0.0562**
		3	0.014	0.007*	0.015	**0.012**
		7	<0.01	<0.01	<0.01	**<0.01**
		10	<0.01	<0.01	<0.01	**<0.01**
	Value corrected for 91% field spike recovery = factor 1.09					

DA1.T = Days after first treatment; DA2.T = Days after second treatment; LOQ = 0.01 µg/cm²
*reported as quantified because sub-plots T1 – T3 are > LOQ and a clear detector signal can be integrated. Average T1 – T3 is > LOQ

Table 80: Dislodgeable Foliar Residue summary in/on wheat for BYF 00587 (bixafen)

Trial N° Country	DA1.T	DA2.T	Plot T1 [µg/cm²]	Plot T2 [µg/cm²]	Plot T3 [µg/cm²]	Mean residues T1-T3 [µg/cm²]
16-2908-01 Belgium	0		0.0830	0.129	0.0800	**0.0973**
	1		0.0687	0.0581	0.0718	**0.0662**
	3		0.0590	0.0597	0.0731	**0.0639**
	7		0.0174	0.0180	0.0216	**0.0190**
	10		0.0148	0.0214	0.0179	**0.0180**
	14	-0	0.0112	0.00803**	0.0106	**0.00994****
		0	0.121	0.0641	0.117	**0.101**
		1	0.0931	0.101	0.0854	**0.0932**
		3	0.0306	0.0202	0.0321	**0.0276**
		7	0.0237	0.0192	0.0198	**0.0209**
		10	0.00911*	0.00985*	0.0115	**0.0102**

DA1.T = Days after first treatment; DA2.T = Days after second treatment; LOQ = 0.01 µg/cm²
*reported as quantified. Subplot T2 is within 95% of LOQ. Subplot T3 + average are > LOQ.
** reported as quantified. Subplot T1 + T3 are > LOQ. Average is at LOQ.

Conclusion

The highest mean value observed in the residue trial were: 0.0878 µg fluopyram /cm² and 0.101 µg bixafen /cm² sampled after the first application. Measured values were corrected for field spike fortification, if the recoveries were below <95% at the relevant concentration. Taking into account an application rate of 0.098 kg per ha this leads to a normalized DFR value of **0.895 µg/cm²/kg/ha fluopyram** and **1.03 µg/cm²/kg/ha bixafen.**

Data Point:	KCP 7.2.3.2/02
Report Author:	[redacted]
Report Year:	2017
Report Title:	Amendment no. 1: Determination of the dislodgeable foliar residues (DFR) of prothioconazole in/on wheat after spray application of JAU 6476 & KWG 4168 EC 460 in the field in Germany
Report No:	12-2901
Document No:	M-455270-02-1
Guideline(s) followed in study:	US EPA OPPTS 875.2100 Foliar Dislodgeable Residue Dissipation (formerly US EPA Pesticide Assessment Guidelines Subdivision K: Reentry Protection, Series 132-1 (a))
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

The purpose of the study 12-2901 was to determine the magnitude of the dislodgeable foliar residues of prothioconazole and JAU 6476-desthio on wheat leaf foliage after each of two spraying applications with JAU 6476 & KWG 4168 EC 460, an EC formulation containing 160 g/L prothioconazole and 300 g/L spiroxamine.

The study included one supervised residue trial conducted in Northern Europe (Germany) during the 2012 season.

The actual application data are presented in the following table. These data reflect the intended application scheme, or, if minor deviations occurred, these were within the acceptable range.

Table 81: Application summary

Trial Number / Country	Crop	Appl. Number	Interval (days)	Growth Stage (BBCH)	Dose rate (L/ha)	Water rate (L/ha)	Appl. rate (kg a.s./ha)	
							Prothioconazole	Spiroxamine
12-2901-01 Germany	Wheat	2	14	47-61	1.25	150	0.2	0.375

Appl. = Application; a.s. = active substance

Representative leaf punch samples were obtained, prepared, identified, transported and stored following the corresponding study plan and EPA OPPTS Guideline 875.2100 (1996).

Eighty leaf disks representing a total area of 200 cm² (double-sided surface) were collected out of the potential worker contact zone including upper, middle, lower, interior and exterior portions of crop foliage after the spray application was dry, according to study schedule. The application equipment used in the study was representative for the crop, the region and the task.

Control samples were collected prior to the first application. Field fortification samples were also generated at the field test site.

Leaf discs were dislodged with a 0.01 % Aerosol OT surfactant solution yielding a total amount of 100 mL of dislodging solution. The dislodging of the leaf samples was performed as soon as possible, but not later than 4 hours after sample collection.

Table 82: General data

EU zone	Outdoor / Greenhouse	Leaf disk area (cm²)	Number of leaf disks	Total surface area (Double-sided surface) (cm²)	Dislodging solution	Amount of dislodging solution (mL)
North	outdoor	1.25	80	200	0.01% Aerosol OT surfactant in tap water	100

Sampling information is given in the report.

Table 83: Information on rainfall events during the study time

Date/Period of Time	Activity	Mean Temp. [°C]	Rainfall [mm]	Sunshine [h]
2012-05-30	treatment, sampling	18	0	9
2012-05-31	sampling	16	6	4
2012-06-02	sampling	13	0	12
2012-06-06	sampling	13	10	2
2012-06-13	treatment, sampling	12	0	0
2012-06-14	sampling	14	0	3
2012-06-16	sampling	16	8	0
2012-06-20	sampling	18	6	2
2012-06-27	sampling	17	5	1
2012-07-04	sampling	22	0	11
2012-07-11	sampling	15	5	1
May 2012		13	45	196
June 2012		16	101	113
July 2012		18	126	168
Climatic data recording was not conducted according to GLP, no irrigation done				

In order to check the performance of the method and the stability of the field samples, recovery determinations were performed from control samples individually spiked with prothioconazole during the field part. The results are presented in following tables:

Table 84: Field Spike Recovery for prothioconazole equivalents (sum of prothioconazole and JAU 6476-desthio)

Crop / Sample material	FL [µg/cm²]	Single values [%]	Mean value [%]	RSD [%]	LOQ [µg/cm²]
Wheat, leaf punch washings	0.005	6; 82; 0	29	-	0.005
	0.05	54; 54; 66	58	11.9	
	1.0	87; 93; 81	87	6.9	
FL = Fortification Level, RSD = Relative Standard Deviation, LOQ = Practical Limit of Quantification These recoveries were performed during the conduct of the study 12-2901. During field phase the field recovery samples were accidently not fortified/stabilized with cysteine hydrochloride					

Table 85: Field Spike Recovery for JAU 6476-desthio

Crop / Sample material	FL [µg/cm²]	Single values [%]	Mean value [%]	RSD [%]	LOQ [µg/cm²]
Wheat, leaf punch washings	0.005	81; 76; 86	81	6.2	0.005
	0.05	96; 94; 90	93	3.3	
	1.0	100; 97; 93	97	3.6	
		Overall Recovery (n = 9)	**90**	**8.8**	
FL = Fortification Level, RSD = Relative Standard Deviation, LOQ = Practical Limit of Quantification These recoveries were performed during the conduct of the study 12-2901.					

Absolut (µg/cm²) DFR of spiroxamine are summarised in the following table. No residues above the LOQ were found in the control samples. Results were corrected for field spike recoveries.

Table 86: Dislodgeable Foliar Residue summary in/on wheat for prothioconazole

Trial N° Country	DA1.T	DAT	Plot T1	Plot T2	Plot T3	Mean average
			[µg/cm²]	[µg/cm²]	[µg/cm²]	[µg/cm²]
12-2901-01 Germany	0		0.105	0.109	0.095	**0.102**
	1		0.021	0.021	0.017	**0.020**
	3		< 0.005	< 0.005	< 0.005	**< 0.005**
	7		< 0.005	< 0.005	< 0.005	**< 0.005**
	14		< 0.005	< 0.005	< 0.005	**< 0.005**
	14	0	0.071	0.067	0.081	**0.072**
	15	1	< 0.005	< 0.005	< 0.005	**< 0.005**
	17	3	< 0.005	< 0.005	< 0.005	**< 0.005**
	22	8	< 0.005	< 0.005	< 0.005	**< 0.005**
	27	13	< 0.005	< 0.005	< 0.005	**< 0.005**
	35	21	< 0.005	< 0.005	< 0.005	**< 0.005**
	42	28	< 0.005	< 0.005	< 0.005	**< 0.005**
	Value corrected for 58% field spike recovery = factor 1.724					
	Value corrected for 29% field spike recovery = factor 3.448					

DA(1.)T = Days after (first) treatment
LOQ = 0.005 µg/cm²
(*)Results are evaluated with Microsoft Excel®, minor deviations may occur when calculating with the presented numbers

Table 87: Dislodgeable Foliar Residue summary in/on wheat for JAU 6476-desthio

Trial N° Country	DA1.T	DAT	Plot T1	Plot T2	Plot T3	Mean average
			[µg/cm²]	[µg/cm²]	[µg/cm²]	[µg/cm²]
12-2901-01 Germany	0		0.111	0.102	0.097	**0.103**
	1		0.078	0.101	0.087	**0.089**
	3		0.011	0.012	0.014	**0.013**
	7		< 0.005	< 0.005	< 0.005	**< 0.005**
	14		< 0.005	< 0.005	< 0.005	**< 0.005**
	14	0	0.127	0.122	0.126	**0.125**
	15	1	0.068	0.068	0.080	**0.072**
	17	3	0.007	0.010	0.011	**0.010**
	22	8	< 0.005	< 0.005	< 0.005	**< 0.005**
	27	13	< 0.005	< 0.005	< 0.005	**< 0.005**
	35	21	< 0.005	< 0.005	< 0.005	**< 0.005**
	42	28	< 0.005	< 0.005	< 0.005	**< 0.005**
	Value corrected for 93% field spike recovery = factor 1.075					
	Value corrected for 81% field spike recovery = factor 1.234					

DA(1.)T = Days after (first) treatment
LOQ = 0.005 µg/cm²
(*)Results are evaluated with Microsoft Excel®, minor deviations may occur when calculating with the presented numbers

Conclusion

The highest mean value observed in the residue trial was 0.102 µg prothioconazole /cm² and 0.125 µg JAU 6476-desthio /cm² sampled after the first application. Measured values were corrected for field spike fortification, if the recoveries were below <95% at the relevant concentration. Taking into account an application rate of 0.2 kg per ha this leads to a normalized DFR value of **0.51 µg/cm²/kg/ha prothioconazole** and **0.625 µg/cm²/kg/ha JAU 6476-desthio.**

Worker exposure calculations (KCP 7.2.4.1)

Fluopyram

Table 88: Worker exposure, Fluopyram, Cereals

Substance	Fluopyram	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.078 kg a.s. /ha	**Spray dilution =** 0.39 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of < 5*10-3Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.05 mg/kg bw/day		RVAAS[2]	mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	
Worker – Inspection, irrigation	Potential exposure mg/kg bw/day		0.0683	% of RVNAS[1]	137%
	Working clothing mg/kg bw/day		0.00764	% of RVNAS[1]	15.3%
	Working clothing and gloves mg/kg bw/day			% of RVNAS[1]	-%
Measured DFR	0.896 µg a.s./cm² per kg a.s./ha				
Worker – Inspection, irrigation (Measured)	Potential exposure mg/kg bw/day		0.0204	% of RVNAS[1]	40.8%
	Working clothing mg/kg bw/day		0.00228	% of RVNAS[1]	4.57%
	Working clothing and gloves mg/kg bw/day			% of RVNAS[1]	-%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Prothioconazole

Table 89: Worker exposure, Prothioconazole, Cereals

Substance	Prothioconazole	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.156 kg a.s. /ha	**Spray dilution =** 0.78 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-2Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.2 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	
Worker – Inspection, irrigation	Potential exposure mg/kg bw/day		0.137	% of RVNAS[1]	68.3%
	Working clothing mg/kg bw/day		0.0153	% of RVNAS[1]	7.64%
	Working clothing and gloves mg/kg bw/day		-	% of RVNAS[1]	-%
Measured DFR	0.51 µg a.s./cm² per kg a.s./ha				
Worker – Inspection, irrigation (Measured)	Potential exposure mg/kg bw/day		0.0232	% of RVNAS[1]	11.6%
	Working clothing mg/kg bw/day		0.0026	% of RVNAS[1]	1.3%
	Working clothing and gloves mg/kg bw/day		-	% of RVNAS[1]	-%

[1] RVNAS = Reference Value Non Acutely toxic active Substance – AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Bixafen

Table 90: Worker exposure, Bixafen, Cereals

Substance	Bixafen	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.078 kg a.s. /ha	**Spray dilution =** 0.39 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-2Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = 25%	**Dermal for in use dilution** = 70%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.13 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	
Worker – Inspection, irrigation	Potential exposure mg/kg bw/day		0.0683	% of RVNAS[1]	52.5%
	Working clothing mg/kg bw/day		0.00764	% of RVNAS[1]	5.88%
	Working clothing and gloves mg/kg bw/day		-	% of RVNAS[1]	-%
Measured DFR	1.031 µg a.s./cm² per kg a.s./ha				
Worker – Inspection, irrigation (Measured)	Potential exposure mg/kg bw/day		0.0235	% of RVNAS[1]	18%
	Working clothing mg/kg bw/day		0.00263	% of RVNAS[1]	2.02%
	Working clothing and gloves mg/kg bw/day		-	% of RVNAS[1]	-%

[1] RVNAS = Reference Value Non Acutely toxic active Substance – AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Prothioconazole-desthio

Table 91: Worker exposure, PTZ-Desthio, Cereals

Substance	PTZ-Desthio	**Formulation =** Soluble concentrates, emulsifiable concentrate, etc.	**Application rate =** 0.141 kg a.s. /ha	**Spray dilution =** 0.705 g a.s./l	**Vapour pressure =** low volatile substances having a vapour pressure of <5*10-3 Pa
Scenario	Cereals, Outdoor, Downward spraying, Vehicle-mounted			**Buffer =** 2-3 m	**Number of applications =** 1 **Application interval =** 365 days
Percentage Absorption	Dermal for product = -%	**Dermal for in use dilution** = 44%	**Oral =** 100%	**Inhalation =** 100%	
RVNAS[1] (AOEL)	0.01 mg/kg bw/day		RVAAS[2]	- mg/kg bw/day	
DFR	3 µg a.s./cm² per kg a.s./ha		DT50	30 days	
Worker – Inspection, irrigation	Potential exposure mg/kg bw/day	0.0778		% of RVNAS[1]	778%
	Working clothing mg/kg bw/day	0.00872		% of RVNAS[1]	87.2%
	Working clothing and gloves mg/kg bw/day	-		% of RVNAS[1]	-%
Measured DFR	0.689 µg a.s./cm² per kg a.s./ha				
Worker – Inspection, irrigation (Measured)	Potential exposure mg/kg bw/day	0.0179		% of RVNAS[1]	179%
	Working clothing mg/kg bw/day	0.002		% of RVNAS[1]	20%
	Working clothing and gloves mg/kg bw/day	-		% of RVNAS[1]	-%

[1] RVNAS = Reference Value Non Acutely toxic active Substance = AOEL
[2] RVAAS = Reference Value Acutely toxic active Substance

Combined exposure

The product is a mixture of 3 active substances. Therefore a combined exposure assessment is provided.

Exposure Assessment of the active substances (Bixafen, Fluopyram, Prothioconazole) in BIX+FLU+PTZ EC 260

Note: The combined toxicological effect of these active substances has not been investigated with regard to repeated dose toxicity.

At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL/RVNAS. This is equivalent to the predicted exposure as % of systemic AOEL/RVNAS to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Table 92: Risk assessment from combined exposure for Operators with PPE

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[2]
Cereals (EFSA with 100% conversion of PTZ to PTZ-desthio)	Fluopyram	0.0593
§§S.CropType§§	Prothioconazole[4]	- -
§§S.CropType§§	Bixafen	0.0228
§§S.CropType§§	PTZ-Desthio	0.138
	Cumulative risk Operators (HI)[1]	**0.22**

[1] HI = Hazard Index
[2] HQ = Hazard Quotient, 75th percentile
[3] HQ = Hazard Quotient, 95th percentile
[4] Considering 100% conversion to PTZ-desthio HQ for PTZ-desthio is considered as the overall worst case

Table 93: Risk assessment from combined exposure for Residents

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[3]	Measured DFR[4]
Adult[1] *Cereals* (EFSA with measured DFR for entry into treated crops)	Fluopyram	0.108	0.0511
§§AdultChild§§[1] *§§S.CropType§§*	Prothioconazole	- -	0.007
§§AdultChild§§[1] *§§S.CropType§§*	Bixafen	0.0417	0.0211
§§AdultChild§§[1] *§§S.CropType§§*	PTZ-Desthio	0.614	0.256
	Cumulative risk Resident – Adult (HI)[2]	**0.764**	**0.335**
Child[1] *Cereals* (EFSA with measured DFR for entry into treated crops)	Fluopyram	0.262	0.159
§§AdultChild§§[1] *§§S.CropType§§*	Prothioconazole	- -	0.0125
§§AdultChild§§[1] *§§S.CropType§§*	Bixafen	0.101	0.0635
§§AdultChild§§[1] *§§S.CropType§§*	PTZ-Desthio	1.48	0.835
	Cumulative risk Resident – Child (HI)[2]	**1.84**	**1.07**

[1] The highest exposure value either from the 75th percentile of each of the four pathways (spray drift, vapour, surface deposits, entry into treated crops) or the sum of the mean exposure values is taken into consideration
[2] HI = Hazard Index
[3] HQ = Hazard Quotient
[4] For measured DFR only entry into treated crops value is taken into consideration

Table 94: Risk assessment from combined exposure for Residents, considering revised default spray drift values from BREAM2

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[3]	Measured DFR[4]
Adult[1] *Cereals* (BREAM2 default for spray drift EFSA for vapour, surface deposits and entry into treated crops with measured DFR)	Fluopyram	0.106	0.0483
	Prothioconazole	- -	0.007
	Bixafen	0.0406	0.02
	PTZ-Desthio	0.599	0.24
	Cumulative risk Resident – Adult (HI)[2]	**0.746**	**0.315**
Child[1] *Cereals* (BREAM2 default for spray drift EFSA for vapour, surface deposits and entry into treated crops with measured DFR)	Fluopyram	0.241	0.138
	Prothioconazole	- -	0.0125
	Bixafen	0.0927	0.0556
	PTZ-Desthio	1.36	0.719
	Cumulative risk Resident – Child (HI)[2]	**1.69**	**0.925**

[1] The highest exposure value either from the 75th percentile of each of the four pathways (spray drift, vapour, surface deposits, entry into treated crops) or the sum of the mean exposure values is taken into consideration
[2] HI = Hazard Index
[3] HQ = Hazard Quotient
[4] For measured DFR only entry into treated crops value is taken into consideration

Table 95: Risk assessment from combined exposure for Residents, considering measurement of exposure for prothioconazole

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[3]	Measured DFR[4]
Adult[1] *Cereals* (FLU+PTZ+BIX EFSA default; PTZ-Desthio measurement of exposure)	Fluopyram	0.108	0.0511
	Prothioconazole[5]	- -	0.007
	Bixafen	0.0417	0.0211
	PTZ-Desthio[6]	0.214	0.214
	Cumulative risk Resident – Adult (HI)[2]	**0.364**	**0.293**
Child[1] *Cereals* (FLU+PTZ+BIX EFSA default; PTZ-Desthio measurement of exposure)	Fluopyram	0.262	0.159
	Prothioconazole[5]	- -	0.0125
	Bixafen	0.101	0.0635
	PTZ-Desthio[6]	0.497	0.214
	Cumulative risk Resident – Child (HI)[2]	**0.86**	**0.449**

[1] The highest exposure value either from the 75th percentile of each of the four pathways (spray drift, vapour, surface deposits, entry into treated crops) or the sum of the mean exposure values is taken into consideration
[2] HI = Hazard Index
[3] HQ = Hazard Quotient
[4] For measured DFR only entry into treated crops value is taken into consideration
[5] Considering 100% conversion to PTZ-desthio HQ for PTZ-desthio is considered as the overall worst case
[6] Measured spray drift exposure adjusted to EFSA default drift values and measured vapoure exposure

With default values proposed by BREAM2 predicted HI is already below 1. This result is further confirmed considering measurement of exposure for prothioconazole-desthio.

Table 96: Risk assessment from combined exposure for Workers

Application scenario	Active Substance	Estimated exposure / AOEL (RVNAS) (HQ)[2]	Measured DFR[3]
Cereals	Fluopyram	0.153	0.0457
	Prothioconazole[4]	- -	0.013
	Bixafen	0.0588	0.0202
	PTZ-Desthio	0.872	0.2
	Cumulative risk Workers (HI)[1]	**1.08**	**0.279**

[1] HI = Hazard Index
[2] HQ = Hazard Quotient
[3] Hazard Quotient, for addition the value of the default DFR is used, when measured DFR not available
[4] Considering 100% conversion to PTZ-desthio HQ for PTZ-desthio is considered as the overall worst case

Considering reasonable steps of refinement it has been demonstrated that the predicted HI is ≤ 1 for all exposure scenarios.

CP 7.3 Dermal absorption

Prothioconazole-desthio

Data Point:	KCP 7.3/01
Report Author:	[redacted]
Report Year:	2020
Report Title:	Prothioconazole-desthio - The in vitro percutaneous absorption of radiolabelled prothioconazole-desthio in a single in-use dilution of the BIX+FLU+PTZ EC 260 formulation through human split-thickness skin
Report No:	786449
Document No:	M-758747-01-1
Guideline(s) followed in study:	OECD Guideline for Testing of Chemicals, Guideline 428: Skin Absorption: In Vitro Method (2004). OECD Environmental Health and Safety Publications Series on Testing and Assessment No. 28, Guidance Document for the Conduct of Skin Absorption Studies (2004). Guidance on Dermal Absorption (EFSA Journal, 2017; 15(6): 4873).
Deviations from current test guideline:	None
Previous evaluation:	No, not previously evaluated
GLP/Officially recognised testing facilities:	Yes, conducted under GLP/Officially recognised testing facilities
Acceptability/Reliability:	Yes

<<M-758747-01-1@S-761199-01-1

Comparative dermal absorption, *in vitro* using rat and human skin

Material and methods

Human skin: Source: Tissue Solutions Ltd and BioIVT.
Number and sex: 4 donors, female.
Anatomical region: Abdomen & thigh.
Thickness: 360 to 400 µm.

Test Material:

Non-radiolabelled: Batch: AE 1194888-PU-03.
Purity = 98.1% w/w.

Radiolabelled: [phenyl-UL-^{14}C]-prothioconazole-desthio.
Batch: KML 9576.
Specific activity: 5.40 MBq/mg.
Radiopurity of the formulation: >98%.

Formulation: The formulation used in this experiment was the BIX+FLU+PTZ EC 260 formulation (specification number 102000027828-03 containing), bixafen (65 g/L), fluopyram (65 g/L) and prothioconazole (130 g/L). It was used at a nominal concentration of for of 0.37 g/L.

Test system: A static diffusion cell system (PermeGear Inc) was used. The static diffusion cells were placed in a manifold on a magnetic stirrer plate heated *via* a circulating water bath to maintain the skin surface temperature at 32°C ± 1°C. The surface area of exposed skin within the cells was 0.64 cm^2. The receptor chamber volume was nominally 5 mL, with each receptor chamber individually marked with the actual volume by the manufacturer.

The receptor fluid was phosphate buffered saline (PBS) containing polyoxyethylene 20 oleyl ether (PEG, *ca* 6%, w/v), sodium azide (*ca* 0.01%, w/v), streptomycin (*ca* 0.1 mg/mL) and penicillin (*ca* 100 units/mL). The receptor fluid was degassed by sonication for 10 min and the pH was confirmed to be 7.48-7.49. Prior to use on the study, the receptor fluid was stored in a refrigerator set to maintain a temperature of *ca* +4°C.

Skin integrity: **Static system**:

Skin samples were allowed to equilibrate at 32°C ± 1°C for *ca* 5 min. Phosphate buffered saline (1 mL) was then added to the donor chamber and the skin samples were allowed to equilibrate for a further *ca* 30 min. The electrical resistance was then measured using a Tinsley Databridge (Model 6401) set at low voltage alternating current, 1000 Hz with a maximum voltage of 300 mV root-mean-squared (rms) in the parallel equivalent circuit mode. Any skin sample exhibiting a resistance less than 7.7 kΩ was excluded from subsequent absorption measurements. The phosphate buffered saline was removed from the skin surface and the skin was rinsed with water and dried with a tissue swab.

Prior to dosing, a 300 µL sample of receptor fluid was removed from the receptor chamber collection arm, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting. The receptor fluid volume was then maintained by the addition of fresh receptor fluid up to the calibration line on the receptor chamber collection arm. Following sample collection, the receptor chamber collection arm was sealed with Parafilm® to prevent evaporation of receptor fluid.

Treatment: The Test Preparation was applied evenly over the entire surface of the exposed *stratum corneum* of 10 split-thickness samples of human skin using a positive displacement pipette calibrated to deliver 6.4 µL (10 µL/cm^2). The donor chambers of the cells were not occluded and so were left open to the atmosphere. Seven representative aliquots of [^{14}C]-PTZ-desthio in Test Preparation were dispensed into vials at the time of dosing, mixed with methanol: scintillation fluid and analysed by liquid scintillation counting.

Sampling: The receptor fluid was collected 1, 2, 4, 8, 12 and 24 h post dose. After the 24 h receptor fluid aliquot was collected, the receptor fluid volume was not maintained with fresh receptor fluid. All the static receptor fluid samples were mixed with methanol:scintillation fluid (1:5, v/v; 12 mL) and analysed by liquid scintillation counting.

The exposure period was terminated at 8 h post dose. Commercial hand wash soap (*ca* 50 µL) was applied to the skin and the soap gently rubbed on the skin with a tissue swab. The skin was then rinsed with 5 mL of a 2% (v/v) commercial soap solution. The soap solution was applied in aliquots (0.5 mL) and each aliquot was aspirated three times with a pipette. The skin was dried with a tissue swab. The process was repeated and the skin was dried with an additional tissue swab

After a 16 h monitoring period, *i.e.* at 24 h post dose, the skin was washed as described above. Following the terminal wash the cells were dismantled and the donor chamber transferred to a pre-weighed pot containing methanol (15 mL). The skin was removed from each cell and placed on a piece of tissue to remove any remaining receptor fluid from the underside of the skin. This

tissue was placed into the receptor chamber wash pot for that particular cell.

The stratum corneum was removed with 20 successive tape strips using D-Squame® disks. The skin sample was rotated 90° after each tape strip. If the epidermis/dermis junction became fragile, the rotation was stopped. Each tape strip was placed into an individual vial containing methanol: scintillation fluid. The skin under the cell flange (unexposed skin) was cut away from the exposed skin. The exposed and unexposed skin samples were placed into separate vials containing Solvable™ (2 mL). The skin samples were placed into a waterbath set to maintain a temperature of *ca* 60°C to aid solubilisation. Stannous chloride solution (0.2 g/mL in ethanol; 500 µL) and scintillation fluid were added to each skin sample.

Donor chambers were left to extract the test item for >30 min before sonication (*ca* 10 min). Following the removal of the apparatus, the samples were split and mixed with scintillation fluid.
The bulk receptor fluid was removed from each receptor chamber, the sample was split and mixed with scintillation fluid. The receptor chambers were then rinsed with methanol (20 mL). This was pooled as a single sample, the samples were split and mixed with scintillation fluid

Radioassay:

All samples were counted together with representative blanks using a liquid scintillation analyser (Packard 2100-TR) with automatic quench correction by external standard. Where scintillation fluid was added to the samples, this was 10 mL. Where methanol: scintillation fluid was added, this was 12 mL. Representative blank sample values were subtracted from sample count rates to give net d.p.m. per sample. Prior to analysis, samples were allowed to stabilise with regard to light and temperature.

Findings:
Prothioconazole-desthio was demonstrated to be sufficiently soluble in the receptor fluid to avoid any risk of back diffusion.

Measurements of the homogeneity of the concentrations of the formulation applied indicated that it was acceptable.

All cells were reported in this study.

The study results are presented in the following Tables.

Table A 1: Mean distribution of radioactivity at 24 hours after dose application of [^{14}C]- prothioconazole-desthio in an EC 260 formulation at the rate of 0.37 g/L to human skin samples: All Cells.

	%dose applied										Human LD Group N = 10 K N°= 0.72	
Sex	Female											
Donor N°	1319	1319	1146	1146	1170	1170	1170	1265	1265	1265		
Sample/Cell N°	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6	Cell 7	Cell 8	Cell 9	Cell 10	Mean	SD
Skin Wash 8 h	50.38	53.46	39.70	37.24	59.25	55.62	62.57	68.79	73.77	68.73	56.95	12.21
Skin Wash 24h	2.42	1.84	1.40	2.17	3.07	4.88	3.39	3.75	4.45	3.66	3.10	1.14
TOTAL SWABS	**52.80**	**55.30**	**41.10**	**39.41**	**62.32**	**60.50**	**65.96**	**72.54**	**78.22**	**72.39**	**60.05**	**13.08**
SURFACE	0.05	0.02	0.03	0.05	0.01	0.02	0.03	0.05	0.08	0.06	0.04	0.02
Donor chamber	0.58	0.07	0.18	0.56	0.19	0.40	0.16	0.15	0.56	0.22	0.31	0.20
Unexposed Skin	0.01	0.03	0.02	0.03	0.08	0.07	0.07	0.04	0.02	0.05	0.04	0.02
TOTAL NON ABSORBED	**53.44**	**55.42**	**41.33**	**40.05**	**62.60**	**60.99**	**66.22**	**72.78**	**78.88**	**72.72**	**60.44**	**13.07**
SKIN	1.70	1.45	3.53	2.46	3.47	1.60	1.21	1.60	0.91	1.23	1.92	0.93
SC 3-5	0.03	0.02	0.02	0.02	0.01	0.01	0.03	0.03	0.03	0.05	0.03	0.01
SC 6-10	0.03	0.02	0.03	0.08	0.01	0.02	0.02	0.04	0.03	0.07	0.04	0.02
SC 11-15	0.03	0.03	0.02	0.04	0.02	0.02	0.02	0.02	0.02	0.05	0.03	0.01
SC 16-20	0.03	0.04	0.03	0.03	0.02	0.02	0.02	0.02	0.03	0.04	0.03	0.01
TOTAL SC 3+	**0.12**	**0.10**	**0.10**	**0.18**	**0.06**	**0.07**	**0.08**	**0.11**	**0.11**	**0.21**	**0.11**	**0.05**
TOTAL DOSE SITE	**1.82**	**1.55**	**3.63**	**2.64**	**3.53**	**1.67**	**1.29**	**1.71**	**1.02**	**1.44**	**2.03**	**0.92**
Receptor fluid (0-12h)	27.99	30.56	30.29	37.24	16.84	23.91	22.13	14.09	11.36	16.92	23.13	8.36
Receptor fluid (0-24h)	36.23	37.10	46.02	51.38	28.66	32.13	28.61	21.41	16.43	22.52	32.05	10.97
%Ratio receptor 12h/24h	77	82	66	72	59	74	77	66	69	75	**72**	**7**
Receptor chamber	1.15	1.03	1.99	1.93	1.27	1.17	1.35	0.83	0.41	1.10	1.22	0.47
TOTAL DIRECT[a]	**37.38**	**38.13**	**48.01**	**53.31**	**29.93**	**33.30**	**29.96**	**22.24**	**16.84**	**23.62**	**33.27**	**11.38**
TOTAL POTENTIAL (dose site+ direct)	**39.20**	**39.68**	**51.64**	**55.95**	**33.46**	**34.97**	**31.25**	**23.95**	**17.86**	**25.06**	**35.30**	**11.95**
TOTAL POTENTIAL (skin excluding SC + direct)	39.08	39.58	51.54	55.77	33.40	34.90	31.17	23.84	17.75	24.85	35.19	11.95
TOTAL RECOVERY	**92.64**	**95.10**	**92.97**	**96.00**	**96.06**	**95.96**	**97.47**	**96.73**	**96.74**	**97.78**	**95.75**	**1.73**
Evaluation according to EFSA Guidance												
Absorption >75% within half of study duration? :	No - (include SC values except SC1 & SC2)											
Recovery <95%? :	No correction needed											
Total % Potentially Absorbable adjusted according to EFSA (2017):	Mean %dose site + %directly absorbed + SD*0.72 = **44**											

[a]: sum of radioactivity found in receptor fluid (0-24h), receptor fluid terminal and receptor chamber.

SD: standard deviation

n: number of skin cells used for calculation

In the above table, the presented means do not always calculate exactly from the presented individual data. This is due to rounding-up differences resulting from the use of the spreadsheet program.

Conclusion:
The dermal penetration through human dermatomed skin of [^{14}C]-prothioconazole-desthio in the EC 260 formulation was investigated at one concentration corresponding to a representative dilution of 0.37 g/L.

Low Dose level (dilution)

The mean percentage of prothioconazole-desthio in the EC 260 formulation that was considered to be potentially absorbable *(directly absorbed plus total remaining at dose site)* over a period of 24 hours for the low dose rate was 44% for human skin when applying the EFSA guidance (2017).

Outside of the EU or other regulated regions where the EFSA 2017 guidance is not applied a mean value of value 35% can be used.

Therefore, the following dermal absorption value can be proposed for use in the non-dietary risk assessments for [^{14}C]-prothioconazole-desthio in the BIX+FLU+PTZ EC 260 formulation:

- 44% for the low dose (0.37 g/L).

CP 7.4 Available toxicological data relating to co-formulants

CONFIDENTIAL information – data provided separately (Document ICP).